FORMULATION DEVELOPMENT AND EVALUATION OF ROSUVASTATIN CALCIUM CONTROLLED RELEASE EFFERVESCENT FLOATING MATRIX TABLETS (GRDDS)

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register no: 26111004

UNDER THE GUIDANCE OF

DR. R.Kumaravelrajan, M. Pharm., Ph.D.
(Institutional Guide)

Mr. T.Sumit Agarwal, M. Pharm.
(Industrial Guide)

DEPARTMENT OF PHARMACEUTICS

C.L.BAID METHA COLLEGE OF PHARMACY

(An ISO 9001-2000 certified institute)

THORAIPAKKAM, CHENNAI-600097

April-2013

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution
Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.
Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF ROSUVASTATIN CALCIUM CONTROLLED RELEASE EFFERVESCENT FLOATING MATRIX TABLETS (GRDDS)"** submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree of **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Register No: 26111004** under my Guidance in the Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

Place: Chennai-97

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
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Place: Chennai -97
Date:

Prof. Dr. GRACE RATHNAM, M. Pharm., Ph.D.,
Principal & HOD,
Department of Pharmaceutics,
C.L.Baid Metha college of Pharmacy,
Chennai-97.

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that the dissertation entitled "Formulation Development and Evaluation of Rosuvastatin Calcium Controlled release Effervescent Floating Matrix Tablets (GRDDS)" is being submitted by Mr. Eguvaputtur Guna Sagar (Reg. No: 26111004) of C.L. Baid Metha College of Pharmacy, Chennai, to the TamilNadu Dr. MGR Medical University, in partial fulfillment for the award of "Master of Pharmacy in Pharmaceutics". The Project work has completed in our organization during 01-July-2012 to 20-Dec-2012.

During this period we found him to be hardworking and committed and we wish him all the best in his future endeavors.

Yours faithfully,

For Sain Medicaments Pvt. Ltd.,

20/12/12

Authorized Signatory

DECLARATION

I hereby declare that the thesis entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF ROSUVASTATIN CALCIUM CONTROLLED RELEASE EFFERVESCENT FLOATING MATRIX TABLETS (GRDDS)"** has been originally carried out by me under the supervision and guidance of **Mr. T.Sumit Agarwal., M. Pharm** (Industrial guide) and **DR. R.Kumaravelrajan, M. Pharm., Ph.D.,** (Institutional Guide) Asst. Professor, Department of Pharmaceutics, C.L. Baid Metha college of Pharmacy, Chennai-97, during the academic year 2012-2013.

Place: Chennai-97

Date:

Register No: 26111004,

Department of Pharmaceutics,

C.L.Baid Metha college of Pharmacy,

Chennai-97.

LIST OF ABBREVIATIONS

API	Active pharmaceutical Ingredient
CI	Compressibility Index
DSC	Differential Scanning Calorimetry
FDDS	Floating Drug Delivery System
FTIR	Fourier transformer infrared spectroscopy
GIT	Gastro Intestinal Tract
GRDDS	Gastro Retentive Drug Delivery System
HCL	Hydrochloric Acid
GRT	Gastric Residence Time
HDL-C	High Density Lipoprotein Cholesterol
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxy Propyl Methyl Cellulose
HR	Hausner Ratio
IP	Indian Pharmacopoeia
LDL-C	Low Density Lipoprotein Cholesterol
MMC	Migrating Myloelectric Cycle
RH	Relative Humidity
TG	Triglycerides
USP	United States Pharmacopoeia
UV	Ultra Violet
WHO	World Health Organisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
mpas	Millipascal seconds
Sec	Seconds

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ACKNOWLEDGEMENT

It is a great time for me to acknowledge those without whom, this work would not have been fruitful.

It gives me an immense pleasure in expressing my deep sense of gratitude to my respected guide **DR. R.Kumaravelrajan, M. Pharm., Ph.D., Assistant Professor,** C.L. Baid Metha college of Pharmacy for his remarkable guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of this work.

I would like to express my immense gratitude to my industrial guide **Mr. T.Sumit Agarwal., M. Pharm., Manager, SAIN MEDICAMENTS Pvt. Ltd,** Industrial Development Area, Uppal, Hyderabad, for providing the great opportunity to carry out the project in **SAIN MEDICAMENTS Pvt. Ltd**, for his valuable guidance and support in each and every aspect of the project.

It is great pleasure and honor for me to owe gratitude to **Dr. Grace Rathnam M. Pharm, Ph.D**. principal for all her support and for giving a valuable guidance and scientific support to carry out this work.

I would like to thank SAIN MEDICAMENTS Pvt. Ltd, for giving me an opportunity to perform my project work in their organization which helped me to mould my project work into a successful one.

I feel proud to express my hearty gratitude and appreciation to all my Teaching and Non-teaching Staff members of **C.L. Baid Metha College of Pharmacy** who encouraged to complete this work.

I feel proud to express my hearty gratitude to all my classmates. Also I want to thank all of those, whom I may not be able to name individually, for helping me directly or indirectly.

Last but not the least I wish to express my deepest sense to respect and love to my parents for their constant support and encouragement throughout.

Register No: 26111004.

DEDICATED TO
MY BELOVED FAMILY
GURU
AND
FRIENDS

1. Introduction

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation etc.[1] During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the Gastro Intestinal Tract (GIT) for a prolonged and predictable period of time exists today.[2] Several approaches are currently utilized in the prolongation of the Gastric Residence Times (GRT) , including Floating Drug Delivery Systems (FDDS), Low- density Systems, Raft Systems incorporating Alginate gels, Bioadhesive or Mucoadhesive Systems, High-density Systems, Super porous Hydrogels and Magnetic systems. The current review addresses briefly about the FDDS that is one of the most leading methodologies in Gastro Retentive Drug Formulations.[3]

Sustained release, Prolonged action, Controlled release, Extended action, Timed release, Depot and Repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.[4] In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the GIT.[5] Sustained release technology is a relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated sustained release drug delivery systems are constantly being developed and tested. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. The drugs, which are toxic or otherwise deleterious in high concentrations in plasma, and thus require controlled administrations of drugs to the patients. Such administration results in a controlled drug concentration.[6]

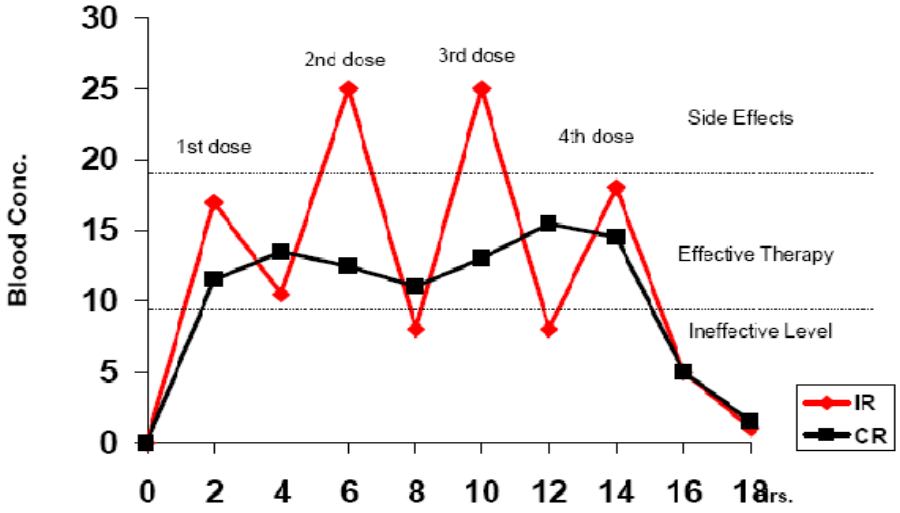


Fig. No. 1: Comparision between Immediate Release and Controlled Release

If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.[7, 8] This is illustrated in the following **Figure No: 2, 3 & 4.**

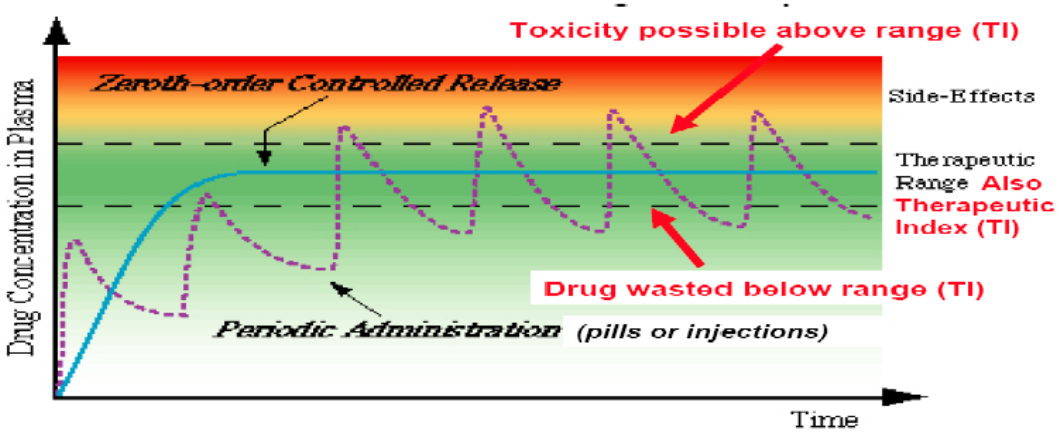


Fig. No. 2: Drug blood levels (µg/ml) versus Time (hr) profiles.

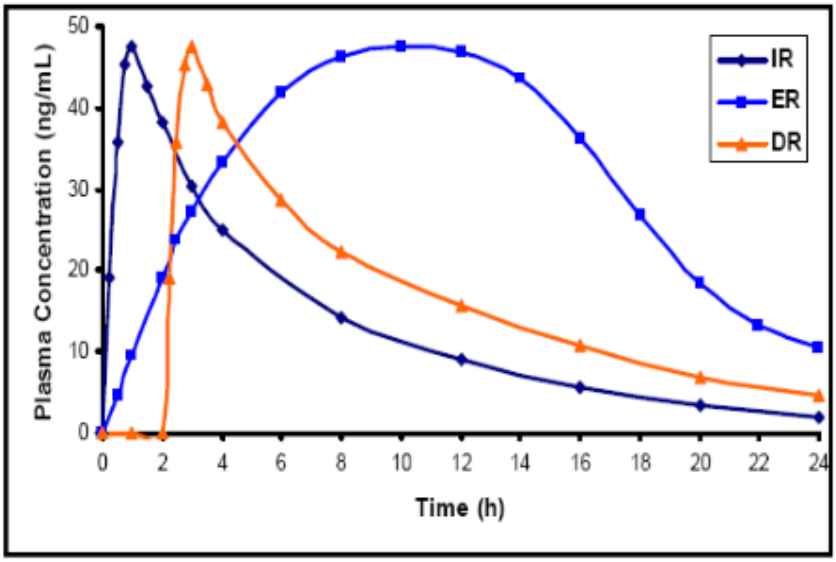


Fig. No. 3: Comparision between various drug release profiles

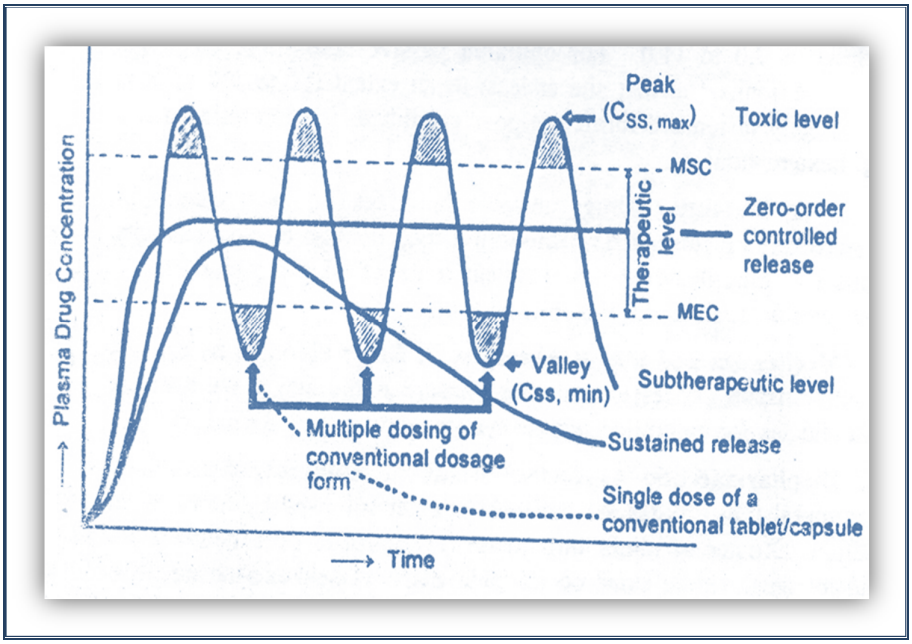


Fig. No. 4: Comparision between various drug release profiles

The difference between controlled release and sustained release is that controlled release is a perfectly zero orderrelease, that is, the drug releases over time irrespective of concentration. Sustained release implies slow release of the drug over a time period, i.e. first order. It may or may not be controlled release.[9]

The following flowchart **(Fig. No. 5)** shows the various approaches used to retain the dosage forms in the gastric region.[10]

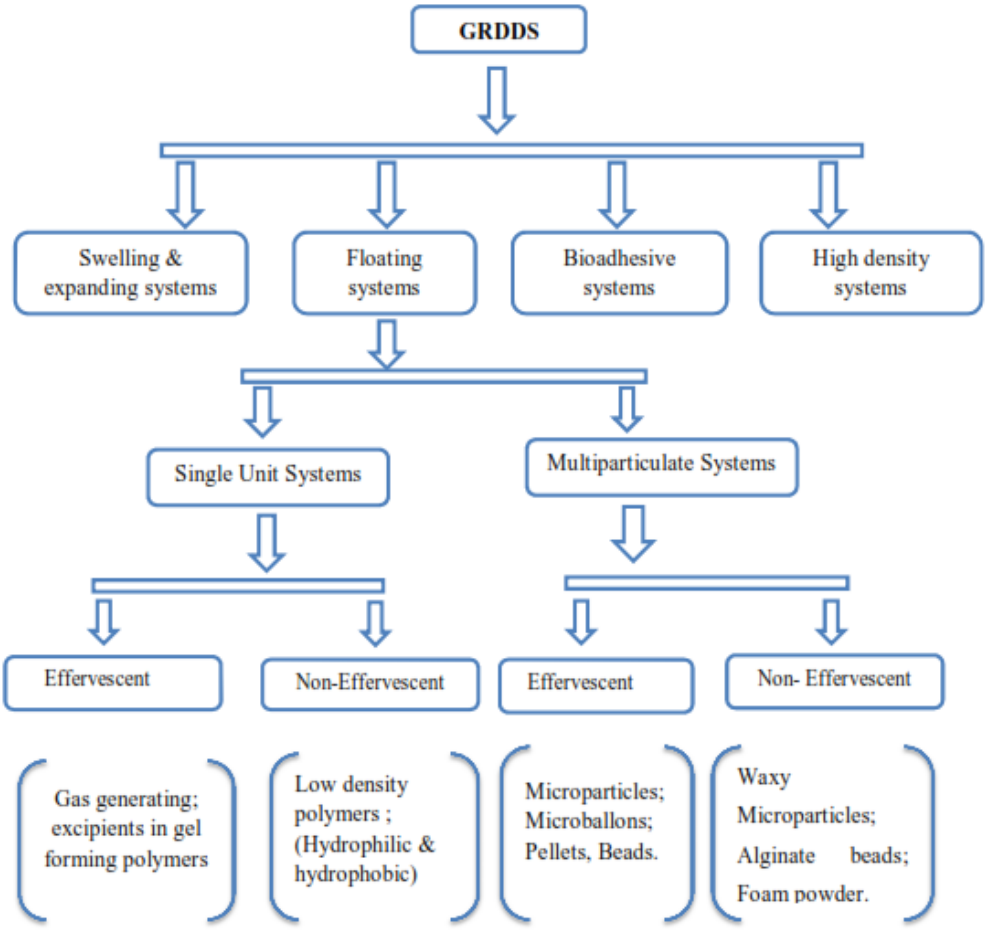


Fig No. 5: Flowchart enlisting various approaches used for designing FDDS

1.1. Drug candidates for GRDDS.[10-12]

Table No.1: Drug candidates for GRDDS

Drug	Pharmaco-logical and/or therapeutic class	Solubility	Stability in gastric and intestinal pH	Absorption & oral bioavailability	Half life (h)
Furosemide	Loop diuretic	Poor water Solubility		Absorbed mostly from the stomach and upper small intestine. Oral bioavailability quite variable (20–60%)	1.3±0.8
Tacrolimus	Immuno-suppressant	Poor water solubility		Low oral Bioavailability	11.3
Captopril	Angiotensin converting enzyme inhibitor	Freely soluble in Water	Stable at gastric pH but unstable in intestine		2
Ranitidine	Histamine H_2-receptor antagonist	Low solubility at alkaline pH	Colonic metabolism	50% absolute Bioavailability	2.5-3
Repaglinide	Oral hypo-glycemic Agent	Poorly soluble in water		Low bioavailability (50%)	1

Itraconazole	Antifungal	Low water solubility		Variable in individuals	21
Metformin Hydrochloride	Antidiabetic	Freely soluble in Water		Absolute bioavailability (50–60%)	1.5-1.6
Trimetazidine Dihydrochloride	Antianginal	Freely soluble in water		Rapidly absorbed	6.0 ±1.4
Ciprofloxacin	Fluoro-quinolone (Antibiotic)	Freely soluble in water		Mainly absorbed in the proximal areas	4
Alfuzosin Hydrochloride	Alpha-adrenergic receptor blocker	Highly water Soluble		Absorb from upper GIT. Absolute bioavailability 49% under fed condition & 25% under fasting condition.	5
Cephalexin	Cephalo-sporin Antibiotic		Degrade in alkaline pH		1
Ofloxacin	Luroqui-nolone antibiotic		Highly soluble in acidic media and precipitates in alkaline	Absorption occurs in upper GIT	8-9

			media		
Metoprolol Succinate	Adrenergic blocking Agent	Highly soluble Through-out physiolo-gical pH		Absorption mainly takes place in the duodenum and jejunum	3- 4
Norfloxacin	Flouroquino-lone Antibiotic	very slightly soluble in water		Mainly absorbed from stomach and upper intestine. Low bioavailability (30–40 %)	3-4
Silymarin	Antioxidant	Poorly water soluble		Low Bioavailability	6
Acyclovir	Antiviral	Slightly soluble in water		Absorb from the duodenum and small intestine; bioavailability 10-20%	1-2
Dipyridamole	Platelet inhibitor	High solubility In acidic		Absorb mainly in upper part of the GIT	2-3

		solution but poor in alkaline media			
Verapamil Hydrochloride	Calcium channel Blocker	Soluble in water		Low bioavailability (10–20%) due to first-pass effect	4
Domperidone	Prokinetic agent	Good solubility in acidic pH but signify-cantly reduced solubility in alkaline medium		Rapidly absorbed from the stomach and the upper part of GIT	7
Zolpidem Tartarate	Non-benzodiazepine& sedative-hypnotic			Absorb from upper part of GIT	

1.2. *Floating drug Delivery System (FDDS):*[13]

Floating drug delivery systems (FDDS) or Hydrodynamically Controlled Systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal . Many buoyant systems have been developed based on Granules, Powders, Capsules, Tablets, Laminated Films and Hollow Microspheres.

The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the Gastro Intestinal Tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by Floating Drug Delivery Systems (FDDS). To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit Hydro Dynamically Balanced Systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems. The Hydrodynamic Balanced System (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents.

Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include: furosemide, cyclosporine, allopurinol ciprofloxacin and metformin. Drugs whose solubility is less in the higher pH of the small intestine (e.g. Chlordiazepoxide and Cinnarizine, the drugs prone for degradation in the intestinal pH (e.g. Captopril), and the drugs for local action in the stomach (e.g. Misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, Catecholamines, Sedative, Analgesics, Anticonvulsants, Muscle Relaxants, Antihypertensive and Vitamins can be administered in HBS dosage form. Drugs reported to be used in the formulation of Floating dosage forms are: Floating microspheres (Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfinadine and Tranilast), Floating granules (Diclofenac sodium, Indomethacin and Prednisolone), Films (Cinnarizine), Floating capsules (Chlordiazepoxide Hydrogen Chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic Acid and Pepstatin) and Floating tablets and Pills (Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin Trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide Mononitrate, Para Aminobenzoic Acid, Piretamide, Theophylline and Verapimil Hydrochloride etc.). Excipients used most commonly in these systems include HPMC, Polyacrylate polymers, Polyvinyl Acetate, Carbopol, Agar, Sodium alginate, Calcium chloride, Polyethylene Oxide and Polycarbonates**.**

1.3. Drug candidates for FDDS.[14]

- ✓ Drugs that have narrow absorption window in GIT (e.g. L-DOPA, Paminobenzoic Acid, Furosemide, Riboflavin)
- ✓ Drugs those are locally active in the stomach (e.g. Misroprostol, Antacids)
- ✓ Drugs those are unstable in the intestinal or colonic environment (e.g. Captopril, Ranitidine HCl, Metronidazole)
- ✓ Drugs that disturb normal colonic microbes (e.g. Antibiotics used for the eradication of Helicobacter pylori, such as Tetracycline, Clarithromycin, Amoxicillin)
- ✓ Drugs that exhibit low solubility at high pH values (e.g. Diazepam, Chlordiazepoxide, Verapamil).

- ✓ Improve bioavailability, minimize total drug quantity, minimize accumulation on chronic use and reduce fluctuation (e.g. Ibuprofen)
- ✓ While the system floats over the gastric contents (GRDDS) it results:
  - ➢ Deliver the drug at controlled and predetermined rate thus maintaining their therapeutic effective concentration in systemic circulation for prolonged periods.
  - ➢ Drug concentration can be controlled with in the narrow therapeutic range by the use of extended release systems, which will minimize the severity of side effects.
  - ➢ Reduces fluctuation in release of drug.
  - ➢ Reduces fluctuation in plasma drug concentration.
  - ➢ Reduces fluctuations of therapeutic effects.
  - ➢ Prolonged Gastric Retention Time (GRT) improves Bioavailability.

1.4. Advantages of FDDS.[15]

- ✓ Effective in delivery of sparingly soluble and insoluble drugs or drugs having low solubility at intestinal pH e.g. Diazepam
- ✓ The Floating systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
- ✓ Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
- ✓ The Floating systems are advantageous for drugs absorbed through the stomach.
  - o e.g. Ferrous salts, antacids.
- ✓ Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
- ✓ It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

- ✓ Facilitates controlled drug administration, which reduces fluctuation in plasma drug concentration and fluctuations of therapeutic effects.
- ✓ Drug concentration can be controlled with in the narrow therapeutic range by the use of extended release systems, which will minimize the severity of side effects.

1.5. Disadvantages of FDDS.[16]

- ✓ Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- ✓ These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
- ✓ The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

1.6. Factors affecting Floating Drug Delivery System.[17]

1.6.1. **Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml).

1.6.2. **Size and Shape:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The

- ➢ Dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per Square Inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.

1.6.3. **Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the Migrating Myoelectric Complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

1.6.4. **Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

1.6.5. **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

1.6.6. **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

1.6.7. **Gender:** Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

1.6.8. **Age:** Elderly people, especially those over 70 years have a significantly longer GRT.

1.6.9. **Posture** : GRT can very between supine and upright ambulatory states of the patients.

1.6.10. **Concomitant drug administration:** Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

1.7. *Requirements for Gastric Retention.*[18]

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

1.8. Formulation of floating dosage form.[19]

The following types of the ingredients can be incorporated in to FDDS:

1.8.1. Hydrocolloids

1.8.2. Inert fatty materials

1.8.3. Release rate accelerants

1.8.4. Release rate retardant

1.8.5. Buoyancy increasing agents

1.8.6. Miscellaneous

1.8.1. Hydrocolloids: Suitable hydrocolloids are synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. e.g. Acacia, Pectin, Agar, Alginates, Gelatin, Casein, Bentonite, Veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydro dynamically balanced to have a bulk density of less than one to assure buoyancy.

1.8.2. Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. e.g. Purified grades of beeswax, fatty acids, long chain alcohols,
glycerides, and mineral oils can be used.

1.8.3. Release rate accelerant: The release rate of the medicament from the formulation can be modified by including excipient like lactose\ and/or Mannitol. These may be present from about 5-60% by weight.

1.8.4. Release rate retardant: Insoluble substances such as Dicalcium phosphate, Talc, Magnesium Strearete decresesd the solubility and hence retard the release of medicaments.

1.8.5. Buoyancy increasing agents: Materials like Ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

1.8.6. Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

1.9. Biological aspects of GRDDS.

1.9.1. Role of GI tract (Stomach).[20]

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

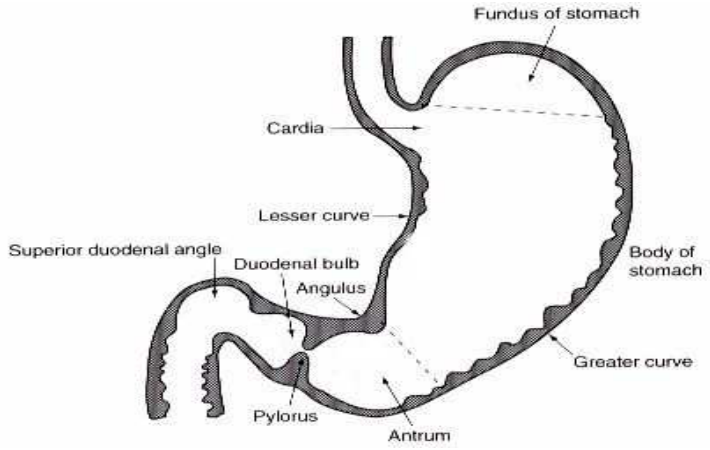


Fig. No. 6: Anatomy of Stomach

The stomach is divided into three anatomical regions. I)Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr.

1.9.2. Gastric motility.[21]

The pattern of motility is distinct in fasted and fed states. During the fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the interdigestive Myloelectric Cycle or Migrating myloelectric Cycle (MMC), which is divided into following 4 phases.

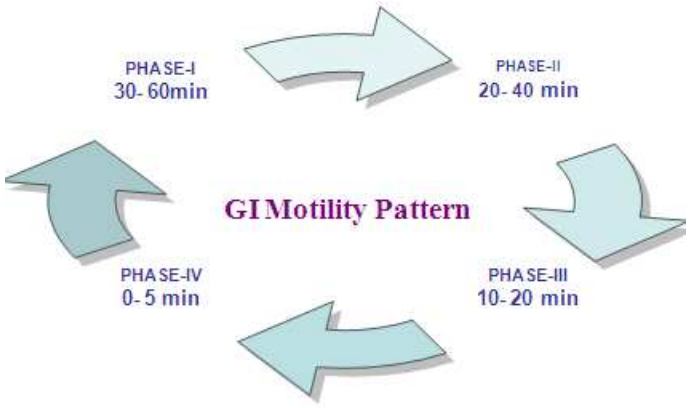


Fig. No. 7: Motility Patterns of the GIT in the Fasted State

- **Phase I (Basal):** Lasts for 30 to 60 minutes. With rare contractions and is characterized by a lack of secretary, electrical, and contractile activity.
- **Phase II (Preburst):** Lasts for 20 to 40 minutes. with intermittent action potential and contractions

- **Phase III (Burst):** Lasts for 10 to 20 minutes. Includes intense and regular contractions. It is due to this wave that all undigested material is swept out of the stomach down to the small intestine. It is also known as housekeeper wave.
- **Phase IV:** Lasts for 0 to 5 minutes.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to fed state. It comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (<1mm), which are propelled toward pylorus. During fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

1.9.3. Gastric emptying.[22]

It can be anticipated that, depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process last from a few minute to 12 hours. Furthermore the relatively brief gastric emptying time in humans which normally averages 2 to 3 hours through the major absorption zone (stomach or upper part of intestine). Particle size and feeding state strongly affect the residence time of particles in the stomach. Some other factors affecting gastric emptying are type of meal and its caloric content, volume, viscosity and co-administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, and carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity and caloric value slows down gastric emptying. Stress increases gastric emptying rate whereas depression slows it down. Females have a slower gastric emptying rate than males. Age and obesity also affect gastric emptying. Gastric emptying of dosage forms is different in fasted and fed conditions.

Table No.2: Transit time of various dosage forms across the segments of the GIT.[23]

	Transit time (hours)

Dosage forms	Stomach	Small intestine	Total
Tablets	2.7	3.1	5.8
Pellets	1.2	3.4	4.6
Capsules	0.8	3.2	4.0
Solution	0.3	4.1	4.4

Table No. 3: Salient Features Of Upper Gastrointestinal Tract.[24]

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption Pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I,E, CM

P – Passive diffusion C – Aqueous channel transport

A – Active transport F – Facilitated transport

I – Ion-pair transport E – Entero-or pinocytosis

CM – Carrier mediated transport

- **Different Features Of Stomach:**

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 ml

Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.

1.10. Mechanism of floating systems.[25]

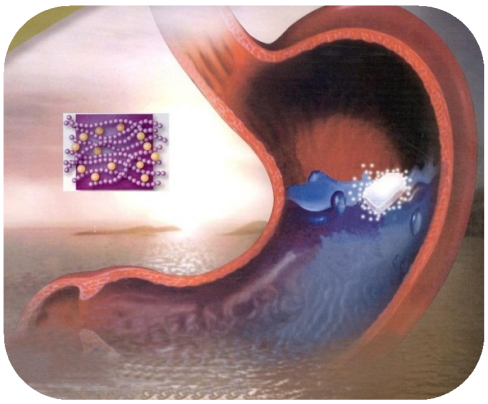


Fig. No. 8: Floating tablet in stomach

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating Drug Delivery Systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure.2 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if "F" is on the higher positive side (**Figure No. 9**). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[26]

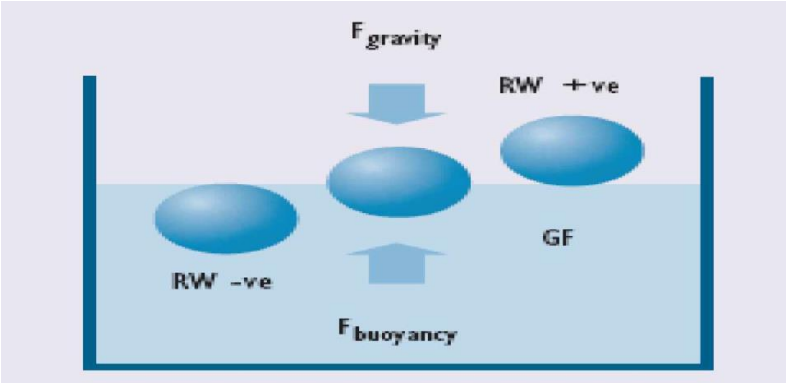


Fig. No. 9: Relation between $F_{gravity}$ & $F_{buoyancy}$

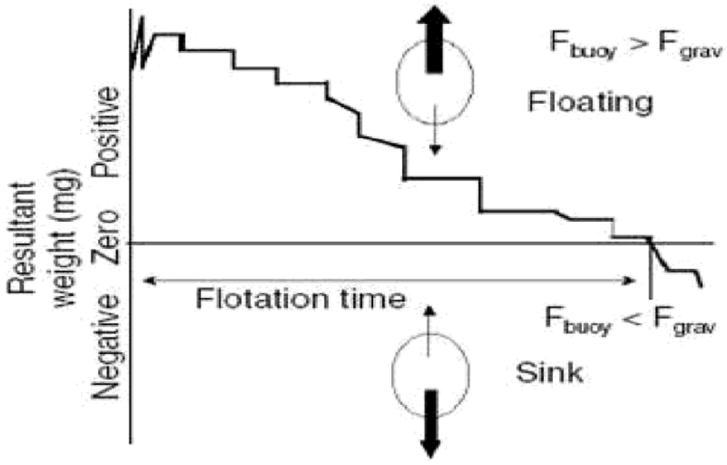


Fig. No. 10: Buoyancy states with resultant weight

$$F = F_{buoy} - F_{grav} = Dfg\ V - Dsg\ V = (Df - Ds)\ g\ V = (Df - M/V)\ g\ V \ldots\ldots\ldots Eq.\ No.\ 1$$

Where,

F = resultant weight of object

Df = Density of Fluid

DS = Density of Solid object

g = Gravitational force

M = Mass of dosage form

V = Volume of dosage form

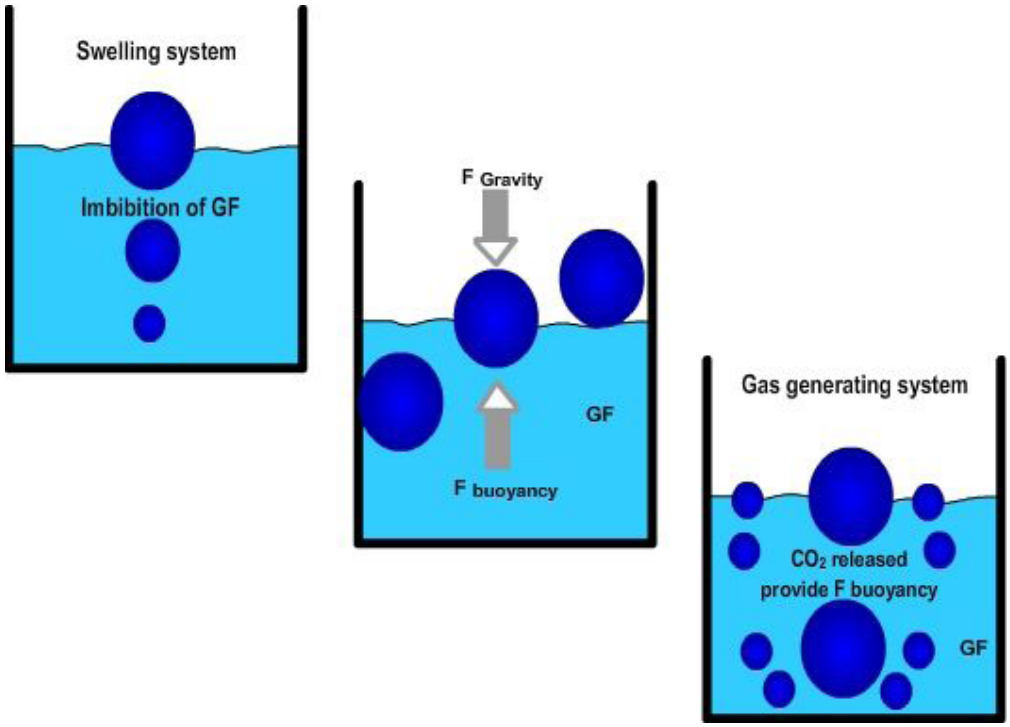


Fig. No. 11: Swelling system, Buoyancy, Gas generating

1.11. *Types of floating drug delivery system.*[27]

Based on the mechanism of buoyancy FDDS can be classified into

1.11.1. Non-Effervescent FDDS

1.11.2. Effervescent FDDS

1.11.3. Raft Forming Systems

These are distinctly different technologies have been utilized in the development of FDDS are:

1.11.1. Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract.The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such

as Polycarbonate, Polyacrylate, Polymethacrylate, Polystyrene as well as Bioadhesive polymers such as Chitosan and Carbopol.

The various types of this system are as:

- ✓ **Single Layer Floating Tablets:** They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

- ✓ **Bi-layer Floating Tablets:** A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach

- ✓ **Alginate Beads:** Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

- ✓ **Hollow Microspheres:** Hollow Microspheres (Microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The Ethanol: Dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The Microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

1.11.2. Effervescent FDDS

- ✓ **Volatile liquid containing system:** The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. Ether, Cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug

made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

- ✓ **Gas-generating Systems:** These buoyant delivery systems or Hydrodynamically Balanced Systems (HBS) utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity, These have a bulk density lower than gastric fluids and making it to float over chime for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

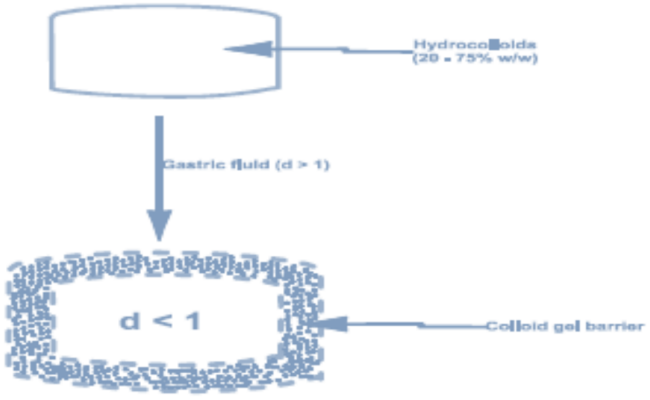


Fig. No. 12: Intra Gastric Single Layer Floating Tablet

- ➢ **Following are types of gas generating GRDDS.[28,29]**
  - **i) Conventional matrix tablets (swellable polymer and effervescent components homogeneously mixed).**
  - **ii) Layered matrix tablets (CR matrix and effervescent components in different layers)**
  - **iii) Core-coated tablets (CR core coated with effervescent components followed on top with a swelling layer)**

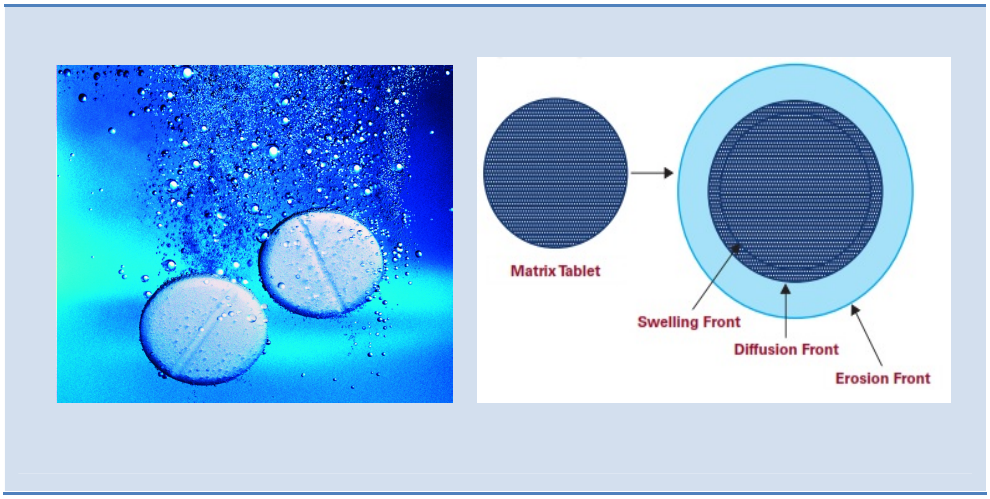


Fig. No. 13: Conventional matrix tablets

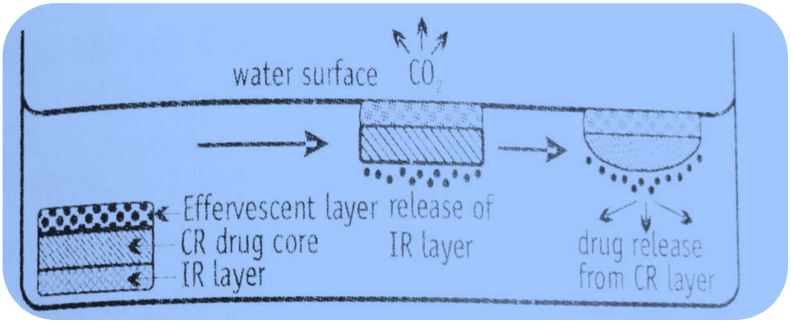


Fig. No. 14: Layered matrix tablets

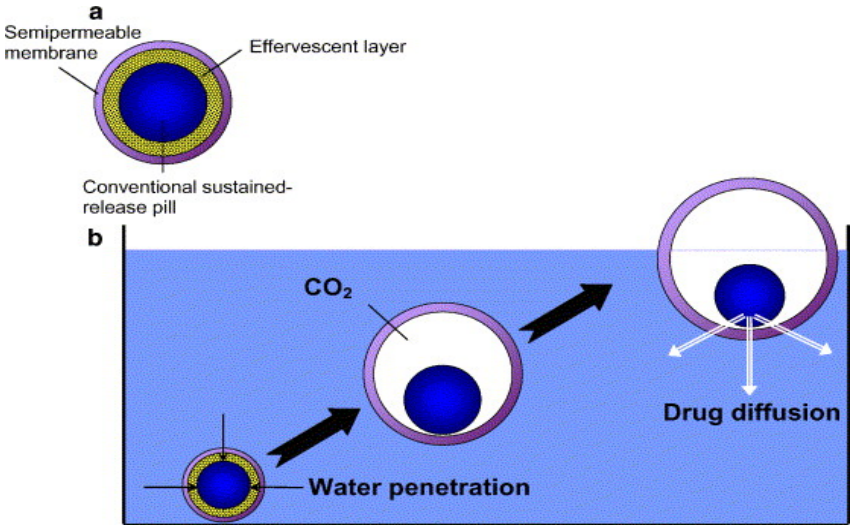


Fig. No. 15: Core-coated tablets

1.11.3. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids.

1.12. Classification of Sustained/Controlled Release Systems.[29]

Table No. 4: Classification of Sustained/Controlled Release Systems

Type of system	Rate-control mechanism
Diffusion controlled ➢ Reservoir system ➢ Monolithic system	Diffusion through membrane
Water penetration controlled ➢ Osmotic system ➢ Swelling system	Transport of water through semi permeable membrane water penetration into glossy polymer
Chemical controlled ➢ Monolithic system ➢ Pendant system ➢ Ion exchange resins	Surface erosion or bulk erosion. Hydrolysis of pendent group and diffusion from bulk polymer. Exchange of acidic or basic drugs with the ions present on resins.
Regulated system	External application of magnetic field or

➢ Magnetic, Ultrasound	ultrasound.

Oral sustained release products have gained importance because of the technological advances, which help achieve zero order release rate of the therapeutic substances. It is not possible to get an ideal sustained effect where the drug is given orally because the rate processes are influenced grossly by a number of factors viz.

- ❖ Variations in pH of the GIT.
- ❖ Gastric motility.
- ❖ Nature of fluid.
- ❖ Fluid volume and content of GIT.
- ❖ Health and disease.
- ❖ *In-vivo* dissolution rate and consequence bioavailability.

1.13. Drug release Kinetics from tablet matrices.[30]

Several kinetics models relating to the drug release from matrices are described below.

1.13.1. Zero-order kinetics:

$$W = k_1 t \ldots\ldots\ldots\ldots\ldots Eq.\ No.\ 2$$

1.13.2. First-order kinetics:

$$\ln (100-W) = \ln 100 - k_2 t \ldots\ldots\ldots Eq.\ No.\ 3$$

1.13.3. Hixon-Crowell"s cube-root equation (erosion model):

$$(100- W)^{1/3} = 100^{1/3} – k_3t……Eq.\ No.\ 4$$

1.13.4. Higuchi's square root of T equation (diffusion model)

$$W = k_4t_{1/2}……..Eq.\ No.\ 5$$

1.13.5. Korsmeyer- Peppas equation (release model):

$$Q_t / Q = K\ t_n……..Eq.\ No.\ 6$$

Where,

W = percent drug release at T; t and k_1 to k_4 are release rate constants, depending on the kinetic model used. The release mechanism of a drug would depend on the dosage form selected, pH and nature of the drug and of course, the polymer used.

1.14. Preparation of matrix devices:[31]

1.14.1. Compression: Matrix tablets can be prepared by the usual tablet compression method. The polymers as well as the drug are mixed intimately and granulated with a granulating fluid (water or alcohol) and the granules compressed into tablets.

1.14.2. Molding: In this procedure the polymer and drug mixture is forced to flow into a closed container having the desired shape by the application of heat and pressure. The closed container is known as the mold. Two types of molding procedure are used.

- **Compression molding:** In this procedure, the polymer and drug mixture is placed in the lower half of a heated mold, the mold is closed, air and excess mixture are forced out and final pressure is applied for the selected T period.
- **Injection molding:** In this procedure, the mixture is first preheated and then forced into a cold mold cavity by means of a hydraulic plunger at pressures ranging between 10,000 psi and 30,000 psi.

1.14.3. Extrusion: In this process, polymer is continuously propelled along a screw through regions of high temperature and pressure where it is melted and compacted and finally forced through a die to give the final shape. In this procedure the polymer and drug mixture is dissolved in a suitable solvent to form a viscous solution that is then spread on a flat, non-adhesive surface; then the solvent slowly evaporates. The resultant polymer is then peeled and milled and the granules are then compressed into tablets.

1.14.4. Polymerization in Situ: In this procedure a liquid polymer or a pre-polymer is used and drug is dispersed in it. By using a polymerizing agent, the monomer drug mixture is polymerized in a suitable mould.

1.15. Mechanism of drug release from matrix devices.[31,32]

There are four systems:

1.15.1 Diffusion-controlled release system

a) Matrix or monolithic systems

b) Reservoir or membrane-controlled systems

1.15.2. Dissolution-controlled release systems

1.15.2. Erosion-controlled release systems

1.15.3. Osmotic- controlled release systems

1.15.1 Diffusion-controlled release system

a) Matrix or monolithic systems

The release rate is normally first-order

$$M = Kt^{-0.5} \text{.....Eq. No. 7}$$

Where,

M = Rate of release,

K = Constant.

In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophillic or a hydrophilic polymer matrix.

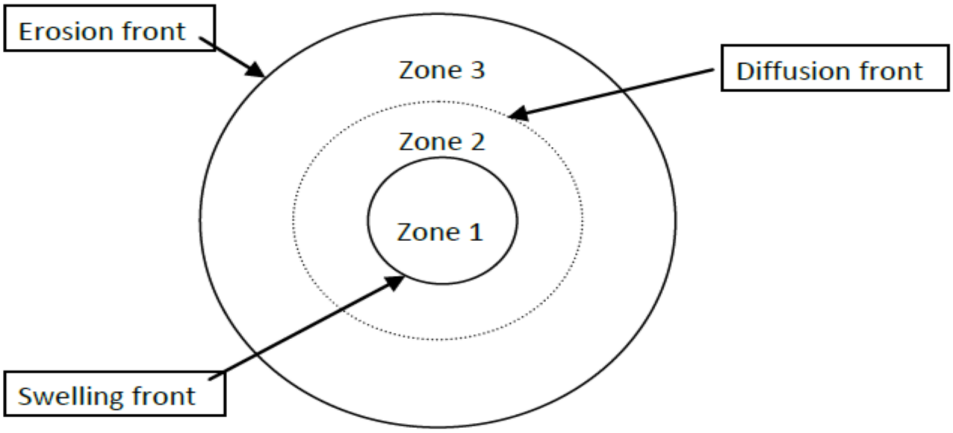


Fig. No. 16: Matrix diffusion controlled drug delivery system

Zone 1: Undissolved drug, glassy polymer layer.

Zone 2: Undissolved drug, gel layer.

Zone 3: Erosion front

Gel layer thickness = Difference between erosion and swelling front position.

Different types of matrices used as oral sustained release drug delivery system i.e.

- Hydrophobic matrix tablet,
- Hydrophilic swellable matrix,
- Floating type drug delivery system (gastro retentive drug delivery system).
- Complex reservoir or multi layered matrix.
- Bioadhasive or mucoadhesive drug delivery system.

- ❖ Beads.
- ❖ Pellets.
- ❖ Microcapsules and micro tablets

According to the generally accepted mechanism, the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with gastrointestinal fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel.

This gel fills the interstices within the tablet, retarding further ingress of liquid. The concentration of polymer within the hydrated layer ranges from dilution at the outer surface to around 90% at the boundary with the drug core. Within this layer, drug in various states of dissolution (undissolved in dilute solution; in saturated solution) is distributed amongst the other ingredients of the tablets. Drug release occurs immediately from the surface (burst effect) followed by diffusion through, and / or erosion of, the hydrated layer. The relative proportions of drug released by diffusion and erosion are determined by the drug's solubility properties and by the physical and chemical nature of the hydrated polymer. This in turn is influenced by other factors, including drug characteristics, dissolution medium and other, which continue to be investigated.

- ✓ **Types of matrixes:**
  - ➢ Lipid matrixes: insoluble lipids (waxes) and soluble channeling agent (sucrose, HPMC)
  - ➢ Non-soluble polymers; polyvinyl acetate, ethyl cellulose and soluble channeling agent (HPMC)
  - ➢ Hydrophilic colloid matrix systems
  - ➢ Usually single unit system, as tablets

- ✓ **Insoluble polymer matrix system:**
  - ➢ Drug is embedded in an inert polymer which is not soluble in GIT fluids.
  - ➢ Drug release similar to leaching from a sponge.Release rate of a drug depends on the degree of porosity and tortuousity of the matrix.

- Posrosity can be modified by addition of channelling agent or soluble excipients
- modifying compaction pressure during tableting

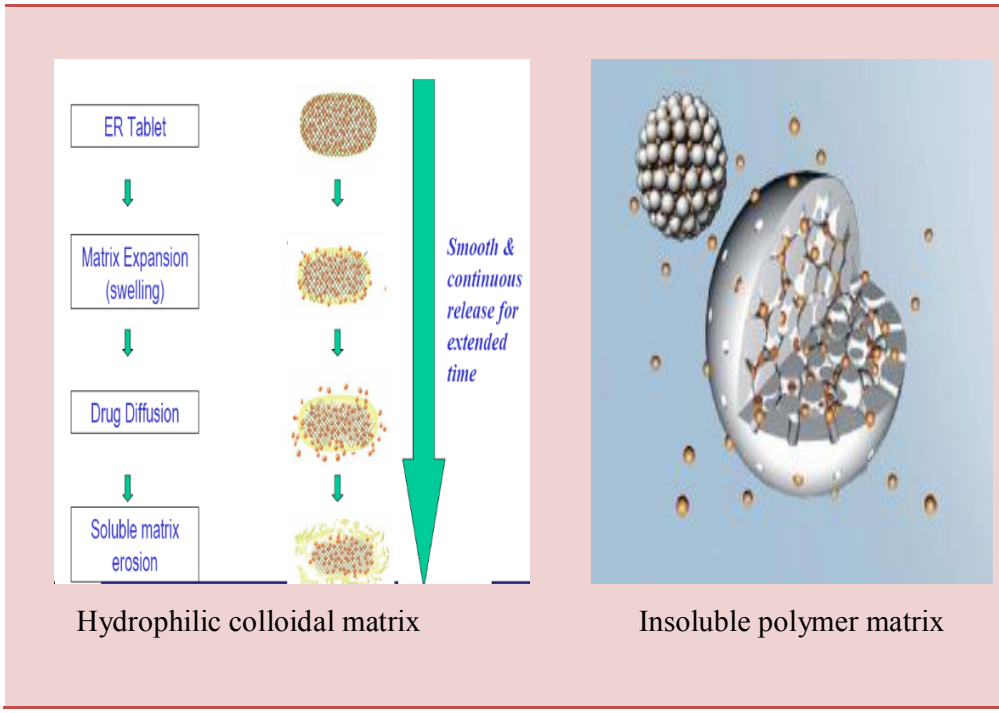


Fig. No. 17: Matrix Diffusion Controlled Mechanism

b) Reservoir diffusion control: In this system water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles or tablet. The rate of the drug release is given by equation.

$$Dm/dt = A\ DK\Delta\ C\ /\ I \ldots\ldots\ldots\ldots Eq.\ No.\ 8$$

Where,

"A" is area,

"D" is diffusion coefficient,

"K" is the partition coefficient of the drug between the membrane and drug core

"I" is the diffusion path length and

"ΔC" is the concentration difference across the membrane.

An important parameter in the above **equation (8)** is the partition coefficient which is defined as the concentration, of the drug in the membrane over the concentration of drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short T so that zero order release will be observed only over a short segment of the T course of drug release. To obtain a constant drug release rate all the terms in right hand side of the **equation (8)** must be held constant. Methods to develop reservoir type devices include press coating, air suspension coating techniques. Micro encapsulation process is a commonly used procedure to coat the drug particles to be incorporated.

1.15.2. Dissolution controlled release:

Controlled release oral products employing dissolution as the rate limiting step are in principle simplest to prepare. Even if a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. We can assume the dissolution process where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate limiting step. In this case the dissolution process at steady state would be described by the Noyes-Whitney equation.

$$dc/dt = KD\ A(Cs - C) \quad \text{.....Eq. No. 9}$$

Where,

"dc/dt" is the dissolution rate

"KD" is the dissolution rate constant

”Cs“is the saturation solubility of the drug and

“C” is the concentration of drug in the bulk of the solution

”A” is the surface area for the drug absorption

In relation to diffusion expression that KD equals D / V.I. Where “D” is the diffusion coefficient, “V” is the volume of the dissolution medium and “I” is the thickness of the unstirred liquid film. From the above expression it can be seen that the rate of dissolution i.e., availability is approximately proportional to the solubility of the drug in the dissolution media (Cs) provided constant area and diffusional path length are maintained.

This equation predicts constant dissolution rate as long as enough drug is present to maintain Cs constant and provided surface area does not change. For spherical particles the change in area can be related to weight of the particle and substituted in the diffusion equation to give and expression that relates dissolution to the weight remaining (W).

$$Wo^{1/3} - W^{1/3} = K_1 D \ldots\ldots\ldots\ldots Eq.\ No.\ 10$$

Where,

“Wo” is the initial weight,

“K_1D” is the cube root dissolution expression.

The above equation described dissolution rate of spherical particles when surface area and diffusion path length are changing.

1.15.3. Erosion-controlled release systems:

Rate of release is controlled by the erosion of a matrix in which the drug is dispersed.It is unite-dose system.Surface erosion is the continuous liberation of matrix material (both drug and excipient) from the surface of the tablet.

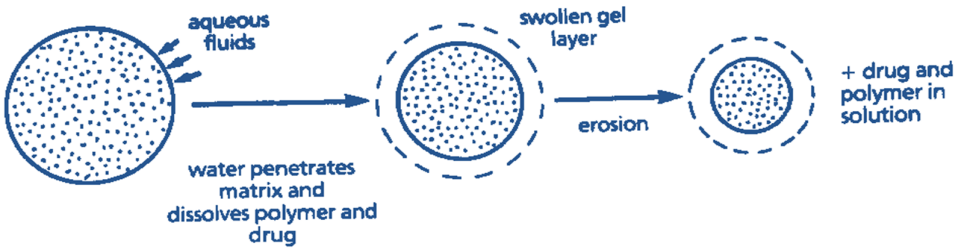


Fig. No. 18: Erosion Mechanism

Mechanism of drug release is a combination of surface erosion and diffusion within the matrix. Drug release can be approximate zero-order.

Materials used in erosion system:

- Lipids or waxes; in which drug is dispersed
- Polymers that gel in contact with water e.g. hydroxypropylcellolose.

1.15.4. Osmotic- controlled release systems

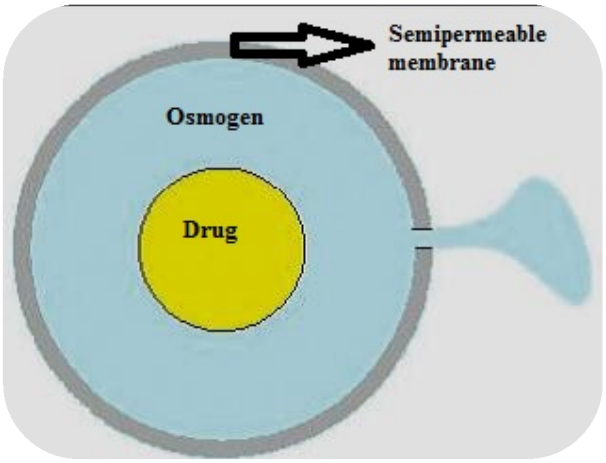


Fig. No. 19: Osmotic- controlled release systems

- **Osmosis:**

Diffusion of fluid through a semipermeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal concentration of fluid on both sides of the membrane.

- **Theory of Osmotic Pump:**

The general expression for the solution delivery rate (dM/dt) from an OP can be described by the following equation:

$$dM/dt = (A/h)\ K\pi.C \quad \text{.....Eq. No. 11}$$

Where,

dM/dt = Drug delivery rate

A = membrane area

h = membrane thickness

π = Osmotic pressure

C = Concentration of compound in the dispersed fluid

1.16. Commonly used drugs in FDDS.[33]

Table No. 5: Commonly used drugs in FDDS

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil,Nicardipine,Nimodipine,piretanide
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, P-nitroaniline, Ibuprofen, Terfenadine, Tranilast ,ketoprofen
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone ,Diltiazem,
Powders	Riboflavin , sotalol ,theophylline
Films	Cinnarizine,Piretanide,Prednisolone,Quinidine guconate

1.17. Marketed preparations of FDDS.[33]

Table No. 6: Marketed preparations of floating drug delivery systems:

Product	Active ingredients
Madopar	Levodopa & Benserazide
Valrelease	Diazepam
Topalkan	Aluminum magnesium
Almagate Flatcoat	Antacid
Liquid Gavison	Alginic acid & bicarbonate
Conviron	Ferrous sulphate
Cifran OD	Ciprofloxacin
Cytochek	Misoprostol

1.18. The enormity of cardiovascular health.[34]

A recent explosion in the amount of cardiovascular risk and incipient, undetected subclinical cardiovascular pathology has swept across the globe. Nearly 70% of adult Americans are overweight or obese; the prevalence of visceral obesity stands at 53% and continues to rise. At any one time, 55% of the population is on a weight-loss diet, and almost all fail. Fewer than 15% of adults or children exercise sufficiently, and over 60% engage in no vigorous activity. Among adults, 11%–13% have diabetes, 34% have hypertension, 36% have prehypertension, 36% have prediabetes, 12% have both prediabetes and prehypertension, and 15% of the population with either diabetes, hypertension, or dyslipidemia are undiagnosed.

About one-third of the adult population, and 80% of the obese, have fatty livers. With 34% of children overweight or obese, prevalence having doubled in just a few years, type 2 diabetes, hypertension, dyslipidemia, and fatty livers in children are at their highest levels ever. Half of adults have at least one cardiovascular risk factor. Not even 1% of the population attains ideal cardiovascular health. Coronary heart disease begins in childhood and progresses throughout life.

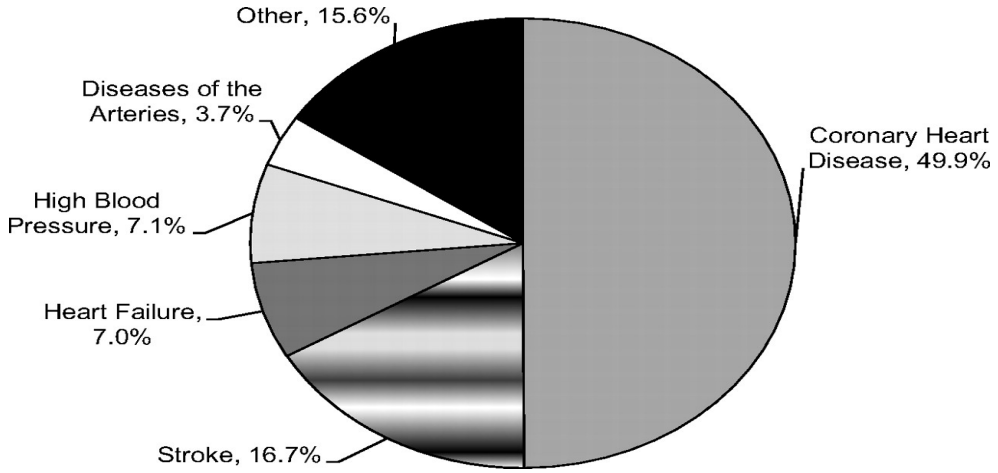


Fig. No. 20: Percentage breakdown of deaths due to cardiovascular disease (United States: 2007)

The National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) emphasizes the need for weight reduction and increased physical activity in the management of mixed dyslipidemia. The use of medications to treat the lipid triad may necessitate the use of lipid lowering agents therapy. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) have a primary effect of lowering LDL-C with a modest effect on lowering TG and raising HDL-C.[35]

2. Literature Review:

1) **N Arunkumar *et al.,*** (2008)[36] aimed at preparing a Floating Drug Delivery System for the model drug Atorvastatin calcium, and evaluating the various processing parameters including the buoyancy studies and *in vitro* drug release studies. Four formulations containing varying proportions of polymers like HPMC K4M and Ethyl cellulose and fixed amount of gas generating agent such as Sodium bi carbonate and hydrophobic meltable material like bees wax were prepared. The tablets were prepared by melt granulation technique and the prepared tablets remained buoyant for more than 8hrs in the release medium. The proportions of the polymers showed significant difference in the release of the drug.

2) **J. Dwivedi *et al.,*** (2011)[37] developed the sustained release Multi-Particulate Pellet Formulation of Rosuvastatin Calcium to improve the distribution of Rosuvastatin calcium, improve the product stability and to modulate the release properties. In the present study sustained release multi-particulate pellet formulation of Rosuvastatin Calcium was prepared by using fluidized bed coating method. Different pellet formulations were made by using sustained release rate controlling polymer like Eudragit NE30D and finally tablets were made. All the Prepared formulations were evaluated for the physical characteristics, *in vitro* dissolution and stability at 40°C/ 75% RH for three months. The release of Rosuvastatin calcium from the tablet for a period up to 16 hrs was recorded in controlled manner.

3) **BK Garg *et al.,*** (2012)[38] developed and evaluated a Pulsatile Drug Delivery System consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Rosuvastatin calcium as model drug were prepared by direct compression of different ratios of Spray-dried Lactose and Microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a Superdisintegrant (Croscarmellose sodium) and an outer rupturable layer of Ethylcellulose. The effect of level of swelling layer was investigated. Rupture and dissolution tests were performed using the USP XXIV paddle method

at 50 rpm in 0.1 N HCl. The lag time of the pulsatile release tablets decreased with increasing levels of swelling layer. Increasing levels of the Ethylcellulose coating retarded the water uptake and thus prolonged the lag time.

4) **D. Krishnarajan *et al.,*** (2012)[39] developed Bio adhesive Gastro Retentive Drug Delivery Systems of Rosuvastatin calcium. It is a lipid lowering drug selective and competitive inhibitor of HMG CoA reductase, which reduces the total number of VLDL and LDL particles .which are designed to increase the gastric residence time, thus prolonging the drug release. In the present study, the tablets were prepared by wet granulation technique, using different natural polymers like Guar gum, Xanthan gum, Karaya gum. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended gastric retention which may result in prolonged absorption. Rosuvastatin calcium Bio adhesive Drug Delivery System showed improved bioavailability and extended release which may favor the reduced dose frequency and improved patient compliance.

5) **Brahma N. *et al.,*** (1999)[40] have reviewed on Floating Drug Delivery Systems: An approach to Oral Controlled Drug Delivery via gastric retention. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short Gastric Residence Times (GRT) and unpredictable Gastric Emptying Times (GET). Several approaches are currently utilized in the prolongation of the GRT, including Floating Drug Delivery Systems (FDDS), also known as Hydrodynamically Balanced Systems (HBS), Swelling and Expanding Systems, Polymeric Bio adhesive systems, Modified-Shape Systems, High-density Systems, and other Delayed Gastric Emptying devices.

6) **A. Streubel, *et al.,*** (2011)[41] studied Floating Matrix tablets based on low density foam powder. The effects of formulation and processing parameters on drug release to develop and physicochemically characterize single unit, Floating Controlled Drug Delivery Systems consisting of (i) Polypropylene Foam Powder, (ii) Matrix-Forming Polymer(s), (iii) Drug, and (iv) Filler (optional). The highly porous foam powder provided low density and, thus, excellent *in vitro* floating

behavior of the tablets. All foam powder-containing tablets remained floating for at least 8 h in 0.1 N HCl at 37 8C. Different types of matrix-forming polymers were studied: Hydroxyl Propyl Methylcellulose (HPMC), Polyacrylates, Sodium Alginate, Corn Starch, Carrageenan, Gum Guar And Gum Arabic. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former.

7) **P.L. Bardonnet, *et al.,*** (2006)[42] have studied Gastro Retentive dosage forms and they explained the overview and special case of Helicobacter pylori. The challenge to develop efficient Gastro Retentive dosage forms began about 20 years ago, following the discovery of *Helicobacter pylori* by Warren and Marshall. In order to understand the real difficulty of increasing the gastric residence time of a dosage form, they summarized the important physiologic parameters, which act upon the gastric residence time, the different drug delivery systems designed until now, i.e. High-Density, Intragastric Floating, Expandable, Superporous Hydrogel, Mucoadhesive And Magnetic Systems, Gastroretentive Dosage Forms especially designed against *H. pylori,* including specific targeting systems against this bacterium.

8) **S. Gopalakrishnan, *et al.,*** (2011)[43] have reviewed Floating Drug Delivery Systems. In the recent years, scientific and technological advancements have been made in the research and development of Novel Drug Delivery Systems by overcoming physiological troubles such as short Gastric Residence Times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including Floating Drug Delivery Systems, Swelling and Expanding Systems, Polymeric Bioadhesive Systems, Modified-Shape Systems, High-Density Systems and other Delayed Gastric Emptying Devices.

9) **Ketan Gulabrao Albhar *et al.,*** (2012)[44] have reported the effect of HPMC K4M, HPMC K15M, Sodium Alginate and Carbopol 934 in the formulation of carbonyl iron capsule. The need of iron therapy prompted present study to develop a formulation of Floating Drug Delivery System of carbonyl irons. Out of the

chosen polymers as HPMC K15M, Sodium Alginate, Carbopol 934 & HPMC K4M the positive and encouraging results in accordance to the aim have been obtained with HPMC K4M and HPMC K15M.Sodium bicarbonate has been used as the gas generating agent to assist to formulation. The formula has been optimized using factorial design. The optimized formulation shows maximum drug release with good floating behavior *in vitro*. The *in vitro* floating behavior has been further confirmed with *in vitro* floating behavior of the same formulation.

10) **Mina Ibrahim Tadros *et al.,*** (2010)[45] were prepared Controlled-Release Effervescent Floating Matrix Tablets of Ciprofloxacin Hydrochloride. Ciprofloxacin Hydrochloride has a short elimination half-life, a narrow absorption window and is mainly absorbed in proximal areas of GIT. They developed a Gastro Retentive Controlled release Drug Delivery System with swelling, floating, and adhesive properties. Ten tablet formulations were designed using Hydroxyl Propyl Methylcellulose (HPMC K15M) and/or Sodium Alginate (Na alginate) as release-retarding polymer(s) and Sodium Bicarbonate (NaHCO3) or Calcium Carbonate (CaCO3) as a gas former. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5 _C. The tablets showed acceptable physicochemical properties. Drug release profiles of all formulae followed non-Fickian diffusion

11) **Amit Kumar Nayak *et al.,*** (2011)[46] were prepared Hydrodynamically Balanced Systems (HBSs) of Ofloxacin using Lactose, HPMC K4M, PVP K 30, and Liquid Paraffin, which may increase the mean residence time in the Gastro Intestinal Tract, and may be able to provide maximum drug at the site of absorption to improve oral bioavailability. All these formulated HBS capsules were floated well over 6 h with no floating lag time. They also showed sustained drug release over 6 hr. Time for 50% release of Ofloxacin was within the range, 2.47 ± 0.02 to 3.07 ±0.08 h. The *in vitro* drug release from these HBS capsules was dependent on HPMC K4M, PVP K 30, and Liquid Paraffin content. The drug release pattern of these HBS capsules containing Ofloxacin followed the Higuchi model with the anomalous transport mechanism.

12) **PD Thahera *et al.,*** (2012)[47] were prepared Gastric Retentive Floating Drug Delivery System (GFDDS) of Norfloxacin as drug candidate, Guar Gum, Sodium CMC, HPMC15 KM along with other excipients like PVP K30 (binder), Sodium Bicarbonate, Microcrystalline Cellulose were used in different concentrations to get the desired controlled release profile over a period of 12 hrs. All the formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and *in vitro* drug release profile. Based on the *in vitro* studies carried out for the optimized formulation by dissolution the performance of the developed formulation promises to be efficient in controlling the drug release rate with the Guar gum , a natural polymer.

13) **Tetsuo Hayashi *et al.,*** (2007)[48] have worked on *in vitro* and *in vivo* sustained-release characteristics of Theophylline Matrix Tablets and novel cluster tablets. They compared the *in vitro*/*in vivo* properties of Theophylline between two sustained-release preparations, which are administered once a day. They conducted a dissolution test with JPXIV *in vitro*, and compared the results between the two preparations. Neither pH nor agitation intensity influenced these preparations. After they were immersed in oleic acid, there were no marked changes in the dissolution properties in the dissolution test. After administration of Tablets A and B containing Theophylline at 200 mg to fasted dogs, we compared plasma level profiles of Theophylline. The mean plasma level of Theophylline gradually increased to a maximum (7.17 _g/mL) 4 h after administration of Tablet A. After administration of Tablet B, a similar finding was noted, with a maximum of 6.09 g/mL. Tablet B showed a higher Coefficient of Variation (CV) for the plasma level at each point.

14) **Ian J. Hardy *et al.,*** (2007)[49] have worked on modulation of drug release kinetics from Hydroxyl Propyl Methyl Cellulose Matrix Tablets using Polyvinyl Pyrrolidone. Hydrophilic Matrix Tablets are widely used to extend the release of a broad range of pharmaceutically active materials. The mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble compounds released

predominantly by diffusion. The swelling and erosion properties of Hydroxyl Propyl Methyl Cellulose (HPMC), typically lead to a first order release rate for water soluble compounds as opposed to the more desirable zero-order kinetics.

15) **Praveen S. Hiremath *et al.,*** (2008)[50] have formulated oral matrix tablet formulations for concomitant Controlled Release of Anti-Tubercular drugs. The aim of the this investigation was to develop Controlled Release (C.R.) matrix tablet formulations of rifampicin and isoniazid combination, to study the design parameters and to evaluate *in vitro* release characteristics. In the present study, a series of formulations were developed with different release rates and duration using hydrophilic polymers Hydroxyl Propyl Methylcellulose (HPMC) and Hydroxyl Propyl Cellulose (HPC). The duration of Rifampicin and Isoniazid release could be tailored by varying the polymer type, polymer ratio and processing techniques. Further, Eudragit L100-55 was incorporated in the matrix tablets to compensate for the pH-dependent release of rifampicin. Rifampicin was found to follow linear release profile with time from HPMC formulations. In case of formulations with HPC, there was an initial higher release in Simulated Gastric Fluid (SGF) followed by Zero Order release profiles in Simulated Intestinal Fluid (SIF) for rifampicin. The release of isoniazid was found to be predominantly by diffusion mechanism in case of HPMC formulations, and with HPC formulations release was due to combination of diffusion and erosion.

16) **Ibrahim El-Bagory *et al.,*** (2011)[51] have worked on formulation and *in vitro* evaluation of Theophylline matrix tablets prepared by direct compression. The deformation mechanism of pharmaceutical powders, used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets. Three polymers of different deformation mechanisms were tested for their impact on Theophylline directly compressed tablets namely Kollidon SR (KL SR, plastic deformation) Ethylcellulose (EC, elastic deformation) and Carnauba wax (CW, brittle deformation) at different compression forces.

17) **Giovanna Corti *et al.,*** (2007)[52] have formulated sustained-release matrix tablets of Metformin Hydrochloride in combination with Triacetyl-b-Cyclodextrin. Different polymers were tested as excipients, i.e. Hydroxyl Propyl

Methylcellulose, Xanthan Gum, Chitosan, Ethylcellulose, Eudragit_L100-55, and Precirol. All the tablets were examined for drug release pattern in simulated gastric and jejunal fluids used in sequence to mimic the GI transit. Release studies demonstrated that blends of a hydrophobic swelling polymer (Hydroxyl Propyl Methyl Cellulose or Chitosan) with a pH-dependent one (Eudragit_L100-55) were more useful than single polymers in controlling drug release. In particular, the 1:1 (w/w) blend of such systems, dispersed in a Eudragit–chitosan polymeric matrix, fully achieved the prefixed goal, giving about 30% released drug after 2 h at gastric pH, and overcoming 90% released drug within the subsequent 3 h in jejunal fluid.

18) **Raghavendra rao n.g *et al.,*** (2009)[53] have worked on Formulation And Evaluation of sustained release matrix tablets of Tramadol Hydrochloride The main objective of the present work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy Propyl Methyl Cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs. Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product.

19) **Hiroyuki Kojima *et al.,*** (2008)[54] have formulated Extended Release of a large amount of highly water-soluble Diltiazem Hydrochloride by utilizing counter polymer in Polyethylene Oxides (PEO)/Polyethylene Glycol (PEG) matrix tablets.

The purpose of this study was to evaluate the feasibility of using a counter polymer in Polyethylene Oxide (PEO)/Polyethylene Glycol (PEG) polymeric matrices for the sustained release of a large amount of highly water-soluble drug. PEO/PEG matrix tablets (CR-A) containing four drugs with different water solubilities were prepared to investigate the effect of drug solubility on the drug-release and diffusion properties of PEO/PEG matrices. Cross-linked Carboxyvinyl Polymer (CVP)/PEO/PEG matrix tablets (CR-B) containing a water-soluble drug, Diltiazem Hydrochloride (DTZ), were also prepared, and their *in vitro* characteristics were compared with those of CR-A. The drug-release rate also increased with the amount of drug loaded. CR-A containing 50% DTZ (by weight) extended drug release by only 6 h. This confirms the difficulty experienced when trying to formulate PEO/PEG matrices for the sustained release of a large amount of highly water-soluble drugs due to large drug diffusion.

20) **Gottimukkala jayapal reddy *et al.,*** (2011)[55] have worked on the development and *in vitro*-in *vivo* behaviour of Nizatidine floating tablets. The tablets were prepared by direct compression method and Hydroxy Propyl Methyl Cellulose (HPMC) of different viscosity grades, Carboxy Methyl Cellulose, Sodium (NaCMC) were incorporated as retarding polymers. Sodium bicarbonate was incorporated as effervescent agent. Formulations were evaluated for weight variation, thickness, hardness, percentage swelling, friability, and *in vitro* drug release, and floating lag time, total duration of floating, dissolution efficacy and *in vivo* Mean Residence Time (MRT) in the stomach. The formulation F6 with HPMC K 4M exhibited floating lag time of less than 1min and floating time of more than 12 hrs. The drug release of the optimized formulation followed Higuchi kinetic model (R2=0.9832) and the mechanism of drug release was found to be super case II according to Krosmeyer-Peppas (n value is 0.60). *In vivo* nature of tablet was observed at different time intervals with help of radiographic pictures in healthy human volunteers and MRT in the stomach was found to be 320 minutes.

3. Aim and Objectives:

There is a considerably evidence to show that the Rosuvastatin calcim – anti lipidemic agent causes rare but severe adverse effects and side effects like Rhabdomyolysis, Myopathy, Kidney toxicity, when it is being administered as Immediate release or Conventional dosage tablets.[6] Hence, the present study aimed to develop and provide Rosuvastatin calcium for controlled release up to 24hrs as the floating matrix dosage form.

The present study aimed to develop the Rosuvastatin calcium floating matrix tablets as a lipid lowering agent. The proposed formulation containing 40mg of Rosuvastatin calcium of 150mg total weight of tablet aimed to control the release up to 24hrs with Zero order kinetics to deliver approximately 0.5mg/hour as administered once a day formulation.

In our study Rosuvastatin calcium used as a model drug and Objectives of the study includes, Development, Characterization, Evaluation of the Floating matrix tablets containing Rosuvastatin calcium. The intended formulation includes various low density polymers such as Xanthan gum, Guar gum, HPMC K4M, HPMC K100M, Carbopol 934P for the prolonged Gastro Intestinal Absorption and to provide buoyancy effect of dosage form. The formulations also to be included Sodium Bicarbonate as a gas generating agent. In order to find out the various drug and polymer interactions in the study, 10 formulations to be prepared containing 20%, 26%, 33% (w/w) with respect to the total tablet weight.

All the formulations to be evaluated the physical characteristics including Friability, Hardness, Weight variation, Drug content uniformity and *In vitro* dissolution. The Swelling Index, Floating duration of tablet dosage form also evaluated separately. All the formulations were fitted with various kinetic models like Zero order, First order, Higuchi, Korsmeyer – Peppas, Hixoncrowell to determine the release mechanism of the formulation. After evaluation of the above parameters of the Rosuvastatin calcium Floating matrix tablets, the effect of the polymers on drug release, Swelling Index and Buoyancy time to be determined by the standard protocol.

4. Plan Of Work:

The present research work relates to design and in vitro evaluation of controlled-release effervescent floating matrix tablets of Rosuvastatin calcium by direct compression technique using Xanthan gum, Guar gum, HPMC K100M and Carbopol 934 as drug release retardant polymers.

4.1. The schematic representation for Plan of Work:

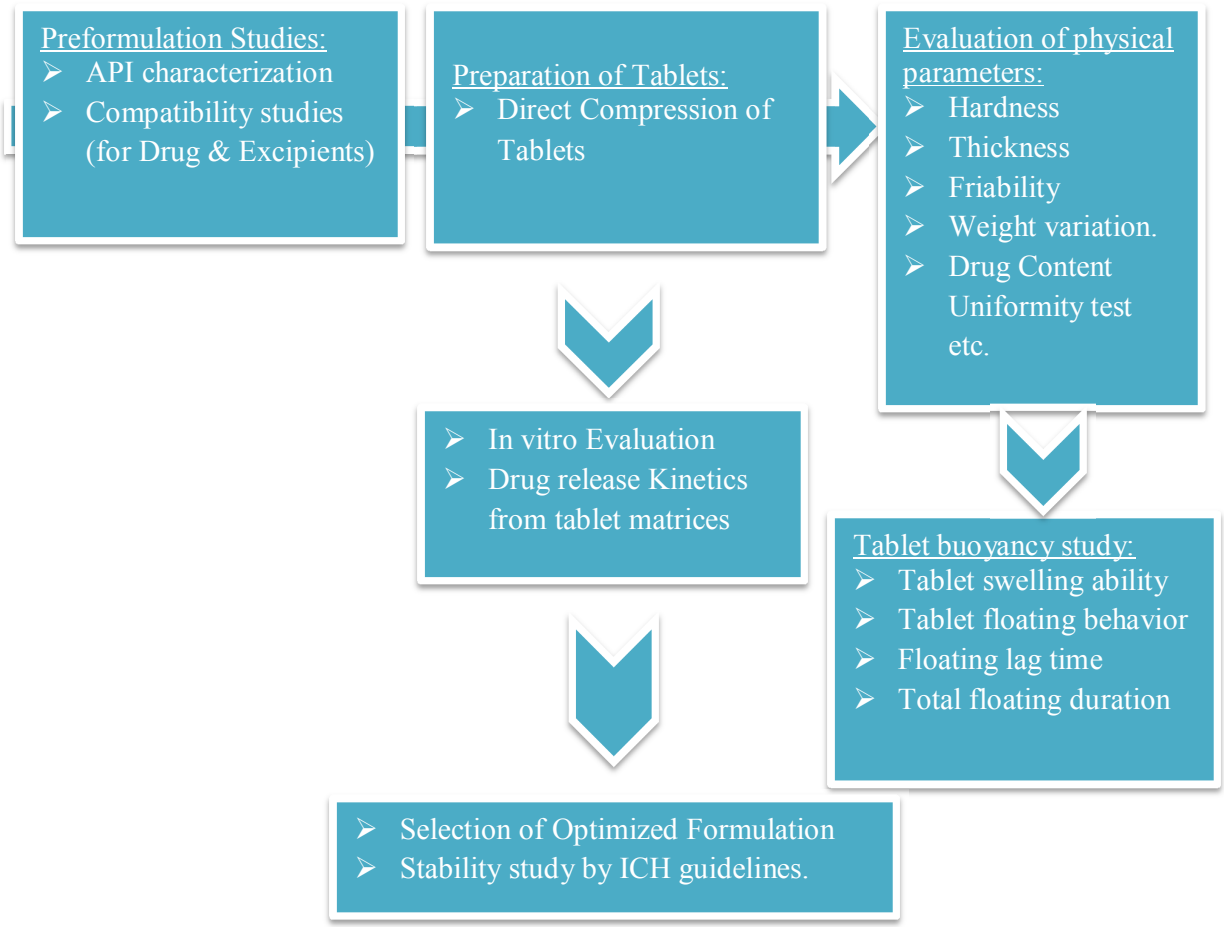


Fig. No. 21: Plan of work schematic representation

5. Drug And Excipient Profile

5.1. Drug profile:

5.1.1. Structure: Rosuvastatin

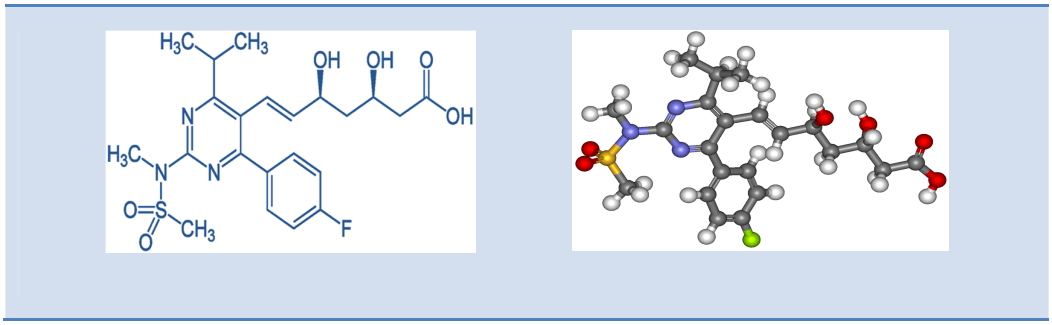


Fig. No. 22: Structure of Rosuvastatin

5.1.2. Structure: Rosuvastatin Calcium

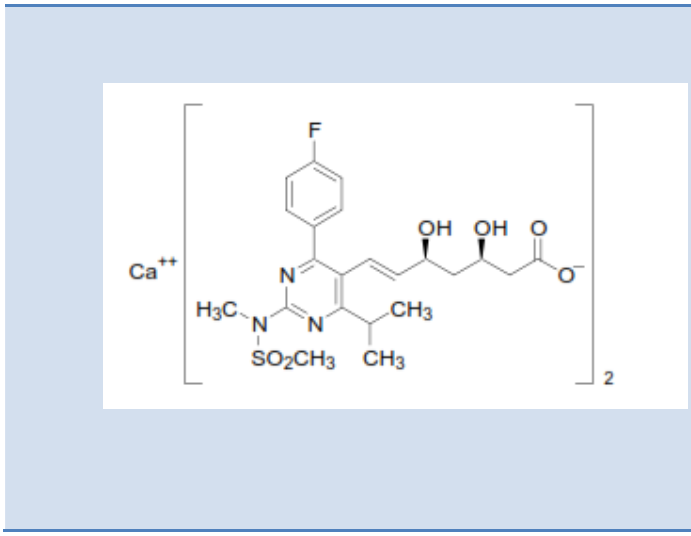


Fig. No. 23: Structure of Rosuvastatin calcium

5.1.3. Systematic (IUPAC) name : (E)-(3R,5S)-7-{4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulphonyl amino)]pyrimidin-5yl}-3,5-dihydroxyhepten- 6-oicacid calcium.

5.1.4. Molecular formula : $C_{22}H_{27}FN_3O_6S.Ca$

5.1.5. Molecular weight : 1001.1

5.1.6. Description : An off- white to creamish white crystalline powder.

5.1.7. Melting Point : 122°c

5.1.8. Solubility : Sparingly soluble in water and methanol, and Slightly soluble in ethanol. Soluble in acetonitrile, and slightly soluble in acetone.

5.1.9. Functional Category : It lowers cholesterol and triglycerides in the blood. This drug may also reduce the risk of heart attack, stroke, or other health problems in patients with risk factors for heart disease.

5.1.10.Storage : Store protected from light and moisture.

5.2. Mechanism of Action:

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-Hydroxy-3-Methylglutaryl Coenzyme A to Mevalonate, a precursor of cholesterol. In vivo studies in animals, and in vitro studies in cultured animal and human cells have shown Rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering.

In in vivo and in vitro studies, Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

5.2.1. Actions:

- ✓ Inhibits HMG-CoA reductase, causing subsequent reduction in hepatic cholesterol synthesis. Reduces serum concentrations of total cholesterol, LDL-cholesterol, VLDL-cholesterol, non-HDL-cholesterol, apo B, and triglycerides; increases HDL-cholesterol concentrations.

- ✓ Statins may slow progression of and/or induce regression of atherosclerosis in coronary and/or carotid arteries, modulate BP in Hypercholesterolemic patients with Hypertension, and possess Anti-Inflammatory activity.

5.3. Pharmacokinetics:

5.3.1. Absorption:

In clinical pharmacology studies in man, peak plasma concentrations of Rosuvastatin were reached 3 to 5 hours following oral dosing. The absolute bioavailability of Rosuvastatin is approximately 20%.

Administration of Rosuvastatin with food did not affect the AUC of Rosuvastatin. The AUC of Rosuvastatin does not differ following evening or morning drug administration.

5.3.2. Onset: Maximal response occurs within 4 weeks.

5.3.3. Duration: Response maintained during continued therapy.

5.3.4. Food: Food decreases rate but not extent of absorption.

5.3.5. Distribution:

Mean volume of distribution at steady-state of Rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations. Crosses the placenta. Distributed into milk in rats, not known whether distributed into human milk.

5.3.6. Metabolism:

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin, which is formed principally by cytochrome P450 2C9, and in vitro studies have demonstrated that N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

5.3.7. Excretion:

Following oral administration, Rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of Rosuvastatin is approximately 19 hours.

After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

5.4. Uses of Rosuvastatin:

The primary uses of Rosuvastatin is for the treatment of Dyslipidemia. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels.

5.5. Dosage and Administration

- ✓ Patients should be placed on a standard lipid-lowering diet before initiation of Rosuvastatin therapy and should remain on this diet during treatment with the drug.
- ✓ Dose varies between 5mg to 40mg (oral) with disease (Dyslipidemias, Primary Hypercholesterolemia and Mixed Dyslipidemia, Homozygous Familial Hypercholesterolemia) and for special population.
- ✓ Administer orally at any time of day without regard to meals. Maximum 40 mg once daily.

5.5.1. **Special Populations:**

- ✓ **Asian Patients:** Initially, 5 mg once daily. When contemplating dosage escalation in patients experiencing inadequate response with 5, 10, or 20 mg daily, consider potential for increased systemic exposure in Asian patients relative to Caucasian patients.
- ✓ **Renal Impairment:** Dosage modification not necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (Cl_{cr} <30 mL/minute) not undergoing hemodialysis: Initially, 5 mg once daily; dosage can be increased up to 10mg once daily.
- ✓ **Lactation:** Distributed into milk in rats; not known whether distributed into human milk. Discontinue nursing or the drug.
- ✓ **Pediatric Use:**
  - ➢ Safety and efficacy not established in pediatric patients. Geriatric Use

- No substantial differences in safety and efficacy relative to younger adults.
- Caution in patients (particularly women) of advanced age (≥65 years of age) and in those with small body frame and frailty.

✓ **Hepatic Impairment:** Use with caution in patients who consume substantial amounts of alcohol and/or have a history of liver disease. (See Contraindications under Cautions.)

✓ **Renal Impairment:** Dosage adjustments necessary in patients with severe renal impairment. (See Renal Impairment under Dosage and Administration.)

5.6. Contraindications:

✓ Active liver disease or unexplained, persistent elevations of serum aminotransferases.

5.7. Warnings/Precautions:

✓ **Fetal/Neonatal Morbidity and Mortality:** Suppression of cholesterol biosynthesis could cause fetal harm. Congenital anomalies following intrauterine exposure to statins reported rarely.

Administer to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking the drug, discontinue therapy and apprise the patient of the potential hazard to the fetus.

✓ **Hepatic Effects:**

- Associated with increases in serum aminotransferase (AST, ALT) concentrations.
- Pancreatitis, Hepatitis, Jaundice, increased serum alkaline Phosphatase concentrations, increased γ-glutamyl transpeptidase concentrations, and increased Bilirubin concentrations reported. Fatty change in liver and rarely, Cirrhosis, fulminant Hepatic Necrosis, and Hepatoma reported with other statins.
- Perform liver function tests before and at 12 weeks after initiation of therapy or any increase in dosage and periodically (e.g., semiannually) thereafter. Patients who develop increased serum AST/ALT concentrations or

manifestations of liver disease should receive frequent liver function tests thereafter until the abnormalities return to normal. If increases in AST or ALT concentrations of >3 times the ULN persist, reduce dosage or discontinue therapy.

- ✓ **Musculoskeletal Effects:**
  - Myopathy (Manifested as muscle pain, Tenderness, or Weakness and serum CK concentration increases >10 times the ULN) reported occasionally.
  - Rhabdomyolysis (Characterized by muscle pain or weakness with marked increases [>10 times the ULN] in serum CK concentrations and increases in S_{cr} [Usually accompanied by brown urine and urinary Myoglobinuria]) reported rarely. Rhabdomyolysis occurs more frequently with 40-mg daily dosage compared with lower dosages. However, risk of Rhabdomyolysis is similar between Rosuvastatin and other statins. In clinical studies, incidence of Myopathy and Rhabdomyolysis increased with dosages >40 mg daily.
  - Risk of Myopathy increased in patients receiving higher doses of statins, in patients with multisystem disease (e.g., renal or hepatic impairment), in patients with concurrent serious infections or hypothyroidism; in patients (particularly women) of advanced age (≥65 years of age), in patients at risk of increased exposure to Rosuvastatin (e.g., Asian patients), in patients with small body frame and frailty, and in patients undergoing surgery (i.e., during perioperative periods). Risk also may be increased by concomitant administration of cyclosporine, niacin, or fibric acid derivatives (e.g., Gemfibrozil).
  - Measure baseline serum CK concentrations prior to initiation of therapy, particularly in black men and patients receiving concomitant therapy with fibric acid derivatives. Obtain serum CK concentrations and compare with baseline concentrations in patients presenting with musculoskeletal symptoms suggestive of Myopathy, because Hypothyroidism may be a predisposing factor, TSH concentrations also should be obtained in such patients. Discontinue if serum CK concentrations increase markedly or if Myopathy is diagnosed or suspected.

- ✓ **Hypersensitivity Reactions:**
  - ➢ Face edema
  - ➢ Vesiculobullous rash
  - ➢ Urticaria and angioedema reported.

5.8. General Precautions:

5.8.1. Role as Adjunct Therapy: Prior to institution of antilipemic therapy, vigorously attempt to control serum cholesterol by appropriate dietary regimens, weight reduction, exercise, and treatment of any underlying disorder that might be the cause of lipid abnormality.

5.8.2. CNS Effects: CNS vascular lesions (e.g., Perivascular hemorrhages and edema, mononuclear cell infiltration of perivascular spaces) observed in animals receiving other statins.

5.8.3. Ocular Effects: Optic nerve degeneration observed in animals receiving other statins.

5.9. Common Adverse Effects:

- ✓ Myalgia,
- ✓ Constipation,
- ✓ Asthenia,
- ✓ Abdominal pain,
- ✓ Nausea.

5.10. Interactions:

Table. no. 7: Drug Interactions:

Drug	Interaction	Comments
Antacids(Aluminum- and Magnesium hydroxide-containing)	Decreased absorption of Rosuvastatin	Administer antacid at least 2 hours after Rosuvastatin
Anticoagulants,oral (e.g. warfarin)	Increased INR	Closely monitor PT until stabilized if Rosuvastatin is initiated or dosage is adjusted in patients receiving a coumarin anticoagulant. Thereafter, monitor PT at intervals usually recommended for patients receiving coumarin anticoagulants
Antifungals, Azoles	Fluconazole: Increased Rosuvastatin concentrations Ketoconazole: Pharmacokinetic interaction unlikely Itraconazole: Increased Rosuvastatin concentrations	Fluconazole: Pharmacokinetic interaction not considered clinically important Itraconazole: Pharmacokinetic interaction not considered clinically important
Bile-acid sequestrants	Enhanced effect on total and LDL-	

	cholesterol	
Cyclosporine	Increased Rosuvastatin concentrations Increased risk of Myopathy	If used concomitantly, Rosuvastatin dosage should not exceed 5 mg daily
Digoxin	Pharmacokinetic interaction unlikely	
Erythromycin	Decreased Rosuvastatin concentrations	Not considered clinically important
Fibric-acid derivatives (fenofibrate, gemfibrozil)	Increased risk of Myopathy and/or Rhabdomyolysis Gemfibrozil: Increased Rosuvastatin concentrations Fenofibrate: Pharmacokinetic interaction unlikely	Gemfibrozil: Concomitant use generally should be avoided If used concomitantly with Gemfibrozil, Rosuvastatin dosage should not exceed 10 mg daily
Niacin	Increased risk of Myopathy and/or Rhabdomyolysis	Weigh benefits against potential risks.
Oral contraceptives	Increased concentrations of Ethinyl estradiol and Norgestrel	

5.11.Specific drugs:

Table No. 8: Interaction with specific drugs:

Drug	Interaction
Colchicine	Increased risk of Rhabdomyolysis with this combination
Cyclosporine	Cyclosporine may increase the serum concentration of Rosuvastatin. Limit Rosuvastatin dosing to 5 mg/day and monitor for changes in the therapeutic and adverse effects of Rosuvastatin if cyclosporine is initiated, discontinued or dose changed.
Fenofibrate	May cause additive Myotoxicity. Monitor for symptoms of muscle toxicity during concomitant therapy.
Gemfibrozil	Gemfibrozil may increase the therapeutic and toxic effects of Rosuvastatin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of Rosuvastatin if Gemfibrozil is initiated, discontinued or dose changed.
Magnesium	Magnesium-containing antacids may decrease the absorption of Rosuvastatin.
Tipranavir	Concomitant therapy of Rosuvastatin and Tipranavir/Ritonavir may increase Rosuvastatin and Tipranavir concentrations. Consider alternate therapy.

5.12. Advice to Patients:

- ✓ Importance of informing patients about risks, especially Rhabdomyolysis, associated with statins alone or combined with other drugs. Importance of patients promptly reporting muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, brown urine, and flu-like symptoms.
- ✓ Importance of adhering to nondrug therapies and measures, including dietary management, weight control, physical activity, and management of potentially contributory disease (e.g., diabetes mellitus).

- ✓ Importance of women informing their clinician if they are or plan to become pregnant or plan to breast-feed. Necessity for clinicians to advise women to avoid pregnancy (i.e., using effective and appropriate contraceptive methods) during therapy and to advise pregnant women of risk to the fetus.

5.13. Available dosage forms:

Table No.9: Available maeketed dosage forms

Product (Tablets)	**Company**
Crestor(10mg,20mg,30mg,4omg)	AstraZeneca
Provisacor(10mg,20mg,30mg,4omg)	AstraZeneca (Italy, Netherlands)
Razel(10mg,20mg,30mg,4omg)	Glenmark (India)
Rosedex(10mg,20mg,30mg,4omg)	Roux-Ocefa (Argentina)
Rosuvas(10mg,20mg,30mg,4omg)	Ranbaxy (India)

5.14. Excipient Profile:

5.14.1. Calcium Phosphate, Tribasic:

- ✓ **Nonproprietary Names:**
  BP: Calcium Phosphate
  PhEur: Calcium Phosphate
  USP-NF: Tribasic Calcium Phosphate
- ✓ **Synonyms**: Calcium orthophosphate, Hydroxylapatite, Phosphoric acid calcium salt (2 : 3), Precipitated calcium phosphate, Tertiary calcium phosphate, Tri-Cafos, Tricalcii phosphas, Tricalcium diorthophosphate, Tricalcium orthophosphate, Tricalcium phosphate.
- ✓ **Empirical Formula and Molecular Weight:** $Ca_3(PO_4)_2$ - 310.20
- ✓ **Functional Category**: Anticaking agent, Buffering agent, Dietary supplement, Glidant, Tablet and capsule diluent.
- ✓ **Applications**: Tribasic calcium phosphate is widely used as a capsule diluent and tablet filler/binder in either direct-compression or wet-granulation processes. It's also used as stabilizing agent for some drugs.
- ✓ **Description**: Tribasic calcium phosphate is a white, odorless and tasteless powder.
- ✓ **Solubility**: Soluble in dilute mineral acids; very slightly soluble in water. Practically insoluble in acetic acid and alcohols.
- ✓ **Stability**: Tribasic calcium phosphate is a chemically stable material, and is also not liable to cake during storage.
- ✓ **Storage conditions**: The bulk material should be stored in a well-closed container in a cool, dry place.
- ✓ **Incompatibilities**: All calcium salts are incompatible with tetracycline antibiotics. Tribasic calcium phosphate is incompatible with Tocopheryl acetate(but not Tocopheryl succinate). Tribasic calcium phosphate may form sparingly soluble phosphates with hormones.

- ✓ **Safety**: Tribasic calcium phosphate is widely used in oral pharmaceutical formulations and food products, and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

5.14.2. Lactose:

- ✓ **Nonproprietary Names:**

  BP: Anhydrous Lactose

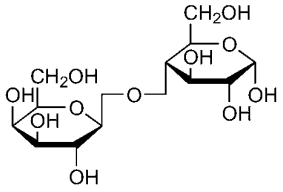
  JP: Anhydrous Lactose

  PhEur: Lactose, Anhydrous

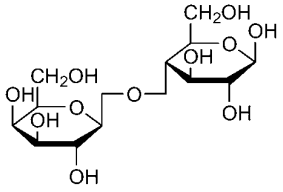
  USP-NF: Anhydrous Lactose

- ✓ **Synonyms**: Anhydrous 60M; Anhydrous Direct Tableting (DT); Anhydrous DT High Velocity; Anhydrous Impalpable; Lactopress Anhydrous; Lactopress Anhydrous 250; lactosum anhydricum; lattosio; milk sugar; SuperTab 21AN; SuperTab 22AN; saccharum lactis.

- ✓ **Structure:**



Anhydrous α-lactose



Anhydrous β-lactose

$C_{12}H_{22}O_{11}$ Mol. Wt. 342.30

Fig. No. 24: Chemical structure of Lactose

- ✓ **Functional Category**: Directly compressible tablet excipient; dry powder inhaler carrier; Lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

- ✓ **Applications**: Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections. Lactose is used to help form tablets because it has excellent compressibility properties. It is also used to form a diluent powder for dry-powder inhalations.

- ✓ **Description**: Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.
- ✓ **Solubility**: Soluble in water; sparingly soluble in ethanol (95%) and ether.
- ✓ **Stability**: Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions.
- ✓ **Storage conditions**: Lactose should be stored in a well-closed container in a cool, dry place.
- ✓ **Incompatibilities**: A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown or yellow-brown-colored products. Lactose is also incompatible with amino acids, amphetamines and Lisinopril.
- ✓ **Safety**: People who are lactose intolerant do not have the enzymes needed to digest Lactose. Most medications do not contain enough lactose to cause lactose intolerance.

5.14.3. Sodium Bicarbonate:

- ✓ **Non-proprietary names:**

  BP: Sodium Bicarbonate
  JP: Sodium Bicarbonate
  PhEur: Sodium Hydrogen Carbonate
  USP: Sodium Bicarbonate

- ✓ **Synonyms:** Baking soda; E500; Effer-Soda; Monosodium carbonate; Natrii hydro-genocarbonas; Sal de Vichy; Sodium acid carbonate; Sodiumhydrogen carbonate.
- ✓ **Chemical name and CAS Registry Number:** Carbonic acid monosodium salt-[144-55-8]
- ✓ **Empirical formula:** NaHCO3
- ✓ **Molecular weight:** 84.01
- ✓ **Functional category:** Alkalizing agent; therapeutic agent.

- ✓ **Melting point:** 270^0C (with decomposition)
- ✓ **Description:** Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste.
- ✓ **Solubility:** Freely soluble in water; practically insoluble inethanol (95%).
- ✓ **Applications:** Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.
- ✓ **Stability and storage conditions:** When heated to about 50°C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, sodium bicarbonate is completely converted into anhydrous sodium carbonate.
- ✓ **Incompatibilities:** In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt.
- ✓ **Safety:** When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material.

5.14.4. Citric Acid:

- ✓ **Non-proprietary names:**

  BP: Citric Acid Monohydrate
  JP: Citric Acid Hydrate
  PhEur: Citric Acid Monohydrate
  USP: Citric Acid Monohydrate
- ✓ **Synonyms:** Acidum citricum monohydricum; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.
- ✓ **Chemical name and CAS Registry Number:** 2-Hydroxy-1,2,3-propanetricarboxylic acid-monohydrate [5949-29-1]
- ✓ **Empirical formula:** $C_6H_8O_7\_H_2O$
- ✓ **Structure:**

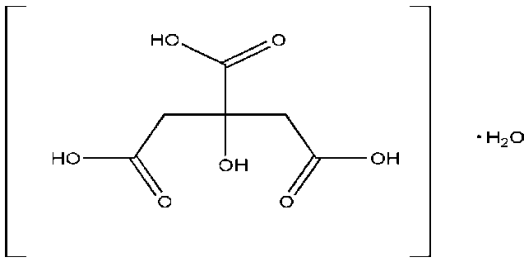


Fig. No. 25: Chemical structure of Citric acid

- ✓ **Molecular weight:** 210.14
- ✓ **Functional category:** Acidifying agent; Antioxidant; Buffering Agent; Chelating agent; Flavor enhancer; Preservative.
- ✓ **Melting point:** ≈100^0C (softens at 75^0C)
- ✓ **Description:** Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.
- ✓ **Solubility:** Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.
- ✓ **Applications:** Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.
- ✓ **Stability and storage conditions:** Citric acid monohydrate loses water of crystallization in dry air or when heated to about 408C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing.

- ✓ **Incompatibilities:** Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

- ✓ **Safety:** Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient.

5.14.5. Magnesium stearate:

- ✓ **Non-proprietary names:**

  BP: Magnesium stearate

  JP: Magnesium stearate

  PhEur: Magnesii stearas

  USPNF: Magnesium stearate

- ✓ **Synonyms:** Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.
- ✓ **Chemical name:** Octadecanoic acid magnesium salt
- ✓ **Structural formula:** [CH3 (CH2)16COO]2Mg
- ✓ **Structure:**

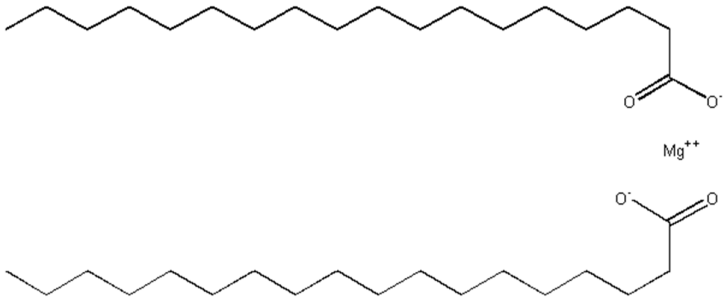


Fig. No. 26: Chemical structure of magnesium stearate.

- ✓ **Molecular weight:** 591.34
- ✓ **Functional category:** Tablet and capsule lubricant.
- ✓ **Melting point:** 117-150^{0}C
- ✓ **Description:** Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.
- ✓ **Solubility:** It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
- ✓ **Applications:** It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets

and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

- ✓ **Stability and storage conditions:** It should be stored in a well closed container in a cool, dry place.
- ✓ **Incompatibilities:** It is incompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing Aspirin, some vitamins and most alkaloidal salts.

5.14.6. Talc:

- ✓ **Nonproprietary Names:**

  BP: Purified Talc

  JP: Talc

  PhEur: Talc

  USP: Talc

- ✓ **Synonyms:** Altalc, Luzenac, Luzenac Pharma, Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite and Superiore.
- ✓ **Chemical name:** Talc
- ✓ **Structure:**

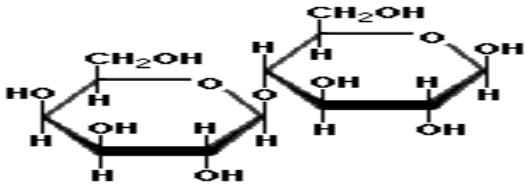


Fig. No. 27: Structure of talc.

- ✓ **Structural formula:** $Mg_6 (Si_2O_5)_4(OH)_4$
- ✓ **Functional Category:** Anticaking agent, Glidant, tablet and capsule diluent and lubricant.
- ✓ **Description:** It is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.
- ✓ **Solubility:** It is practically insoluble in dilute acids and alkalis, organic solvents and water.

- ✓ **Applications:** It was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as dissolution retardant in the development of controlled release products. In topical preparations, it is used as a dusting powder, although it should not be used to dust surgical gloves. It is a natural material; it may frequently contain micro-organisms and should be sterilized when used as a dusting powder. It is additionally used to clarify liquids and is also used mainly for its lubricant properties, in cosmetics and food products.
- ✓ **Stability and storage conditions:** It is a stable material and may be sterilized by heating at 160C for not less than 1 hr. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well closed container in a cool, dry, place.
- ✓ **Incompatibilities:** It is incompatible with quaternary ammonium compound.

5.15. Polymer Profile:

5.15.1. Carbomer 934P:

- ✓ **Nonproprietary Names:**

  BP: Carbomers

  PhEur: Carbomers

  USP-NF: Carbomer

Note that the USP32–NF27 contains several individual carbomer monographs.

Applicable synonyms for Carbopol 934P NF polymer are carboxypolymethylene and carbomers. Carbomers are carboxyvinyl polymers of extremely high molecular weight that are available as dry fluffy powders. Various grades of carbomers are commercially available that different from each other depending on their molecular weight and a architecture as well as on the use of either allyl sucrose or allyl ethers of pentaerythritol for cross-linking acrylic acid. The chemical structure of carbomer is illustrated in **Fig. No. 6.**

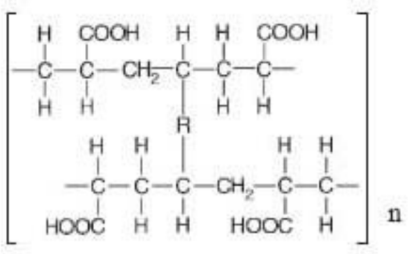


Fig. No. 28: The structure of Carbopol (R= allylsucrose or allyl pentaerythritol)

Carbomer resins intended for oral and mucosal applications are designated by a 'P' (934P, 974P, 971P). They contain between 56-58% of the carboxylic groups calculated on dry basis. A high percentage of carboxylic acid groups allow the polymer to be water swellable. When dispersed in water, carbomer resin molecules partially swell and become viscous. On neutralization with a water-soluble base, the resin molecules swell completely, with a dramatic increase in their viscosity

- ➢ **Physical and Chemical Properties of Carbopol :**

Table No. 10: Physical and Chemical Properties of Carbopol

Appearance	Fluffy, white, mildly acidic polymer
Bulk Density	Approximately 208 kg/m ^{3} (13 lbs. ft ^{3})
Specific gravity	1.41
Moisture content	2.0% maximum

Equilibrium moisture content	8-10% (at 50% relative humidity)
PKa	6.0 ± 0.5
pH of 1.0% water dispersion	2.5 - 3.0
pH of 0.5% water dispersion	2.7 - 3.5
Equivalent weight	76 ± 4
Ash content	0.009 ppm (average)
Glass transition temperature	100-105 ^{0}C (212-221 ^{0}F)

The original oral Carbopol polymer, 934P NF, has been used in oral suspensions worldwide since the mid 1960s. Carbopol 974P NF polymers have similar rheological properties to Carbopol 934P NF: both are highly cross-linked polymers that produce mucilages with very short flow rheology. Short flow rheology can be characterized as a gelled consistency similar to mayonnaise. Carbopol 971P NF polymers, lightly cross-linked polymers, provide very low viscosities and excellent yield values at low usage levels. Suspensions formed with Carbopol 971P NF polymers will have longer rheology and will flow like honey. Carbopol 71G polymers, a granular form of 971P NF polymers, will give the same viscosity and rheology as 971P NF, but are easier to handle and disperse.

- ✓ **Functional Category:** Bio adhesive material; controlled-release agent; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.
- ✓ **Description:** Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor. A granular carbomer is alsoavailable (Carbopol 71G).
- ✓ **Controlled-Release & Solid Dosage Applications of Carbopol:** Although Carbopol polymers have enjoyed success in controlled-release solid dose formulations since the 1960s, the number of companies developing and commercializing controlled-release tablets using Carbopol and Noveon polymers has increased significantly in recent years. In response to this commercial interest, we have tested a variety of excipients and active drug ingredients in tablet models using both direct-compression and wet granulation methods. These polymers can be successfully formulated into a

variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics.

Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%) and feature extremely rapid and efficient gelation characteristics under both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) test conditions. They also produce tablets of excellent hardness and low friability over a range of compression forces, as well as demonstrably longer dissolution times at lower concentrations than other controlled-release excipients. Greater formulating latitude in dosage forms is therefore possible using Carbopol polymers as the functional controlled-release excipient.

- ✓ **Incompatibilities:** Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes.

- ✓ **Safety:** Carbomers are generally regarded as essentially nontoxic and nonirritant materials.

5.15.2. HPMC K-100 M:

- ✓ **Nonproprietary Names:**
  BP: Hypromellose
  JP: Hydroxy Propyl Methyl Cellulose
  PhEur: Hypromellosum
  USP: Hypromellose

- ✓ **Synonyms:** Benecel MHPC; E464; Hydroxyl Propyl Methyl Cellulose;HPMC; Methocel;Methylcellulose Propylene Glycol Ether; methyl Hydroxy Propyl Cellulose; Metolose; Tylopur.
- ✓ **Chemical Name and CAS Registry Number:** Cellulose hydroxypropyl methyl ether [9004-65-3].
- ✓ **Structural Formula:**

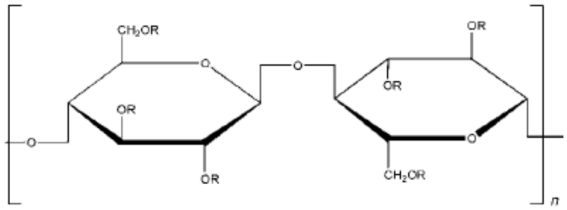


Fig. No. 29: Chemical structure of HPMC K-100M

Where,

" R" is H, CH_3, or $CH_3CH(OH)CH_2$

- ✓ **Functional Category:** Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.
- ✓ **Description:** Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.
- ✓ **Physical and Chemical Properties:**
- ✓ **Acidity/alkalinity:** pH = 5.0–8.0 for a 2% w/w aqueous solution.
- ✓ **Ash:** ≤1.5%
- ✓ **Autoignition temperature**: 360^0C
- ✓ **Density (bulk):** 0.341 g/cm^3
- ✓ **Density (tapped):** 0.557 g/cm^3
- ✓ **Density (true):** 1.326 g/cm^3
- ✓ **Melting point:** Browns at 190–200^0C; chars at 225–230^0C.
- ✓ **Glass transition temperature** : 170–180^0C.
- ✓ **Moisture content:** Hypromellose absorbs moisture from the atmosphere.The amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
- ✓ **Viscosity:** 2% (w/v) aqueous solutions of Methocel K100M - 100 000mPas
- ✓ **Solubility**: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol(95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane,and mixtures of water and alcohol.
- ✓ **Applications in Pharmaceutical Formulation or Technology:** Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In

oral products, hypromellose is primarily used as a tablet binder,(1) in film-coating,(2–7) and as a matrix for use in extended-release tablet formulations.(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with Methylcellulose, Hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, Hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

- ✓ **Incompatibilities:** Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.
- ✓ **Stability and Storage Conditions:** Hypromellose powder is a stable material, although it is hygro-scopic after drying. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.
- ✓ **Safty:** Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have alaxative effect.

5.15.3 Xanthan Gum:

- ✓ **Nonproprietary Names:**

  BP: Xanthan Gum

PhEur: Xanthan Gum

USP-NF: Xanthan Gum

- ✓ **Synonyms:** Corn sugar gum, E415, Keltrol, polysaccharide B-1459, Rhodigel; Vanzan, NF, Xantural.Chemical
- ✓ **Name and CAS Registry Number:** Xanthan gum [11138-66-2]
- ✓ **Chemical structure:**

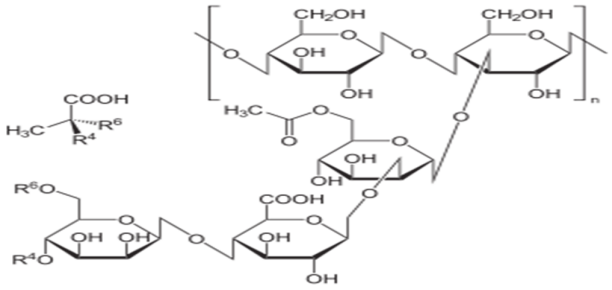


Fig. No. 30: Chemical structure of Xanthan gum

- ✓ **Molecular formula:** $C_{35}H_{49}O_{29}$ (monomer)
- ✓ **Molecular mass** : 933(monomer)
- ✓ **Odour** : slight odour
- ✓ **Colour** : white to cream coloured free flowing powder
- ✓ **Taste** : Tasteless
- ✓ **Functional Category**: Stabilizing agent; suspending agent; viscosity-increasing agent.
- ✓ **Structural features:** Each xanthan gum repeat units contains five sugar residues: two Glucose, two Mannose, and one Glucuronic Acid. The polymer backbone consists of four b-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan from cellulose.

- ✓ **Physical and Chemical Properties:**
  - ➢ **Acidity/alkalinity:** pH = 6.0–8.0 for a 1% w/v aqueous solution.
  - ➢ **Freezing point:** 0^0C for a 1% w/v aqueous solution.
  - ➢ **Heat of combustion:** 14.6 J/g (3.5 cal/g)
  - ➢ **Melting point:** Chars at 270^0C.
  - ➢ **Refractive index n_D^{20}:** 1.333 (1% w/v aqueous solution).
  - ➢ **Solubility:** Practically insoluble in ethanol and ether; soluble in cold or warm water.

- **Specific gravity:** 1.600 at 25^0C
- **Viscosity (dynamic)**: 1200–1600 mPa s (1200–1600 cP) for a 1%w/v aqueous solution at 25^0C.

✓ **Pharmaceutical Applications**:

Primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Controlled-release tablets of Diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictable manner, and the drug release profiles of these tablets were not affected by pH and agitation rate. Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation.It has also been used in combination with Chitosan, Guar Gum, Galactomannan and Sodium alginate to prepare sustained-release matrix tablets.

Xanthan gum has been used as a binder, and in combination with Konjac glucomannan is used as an excipient for controlled colonic drug delivery. Xanthan gum with boswellia(3 : 1) and guar gum (10 : 20)have shown the best release profiles for the colon-specific compression coated systems of 5-fluorouracil for the treatment of colorectal cancer. Xanthan gum has also been used with guar gum for the development of a floating drug delivery system.It has also has derivatized to sodium carboxymethyl xanthan gum and crosslinked with aluminum ions to prepare microparticles, as a carrier for protein delivery.

✓ **Stability and Storage Conditions:** Xanthan gum is a stable material. Aqueous solutions are stable overa wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60^0C. The bulk material should be stored in a well-closed container in a cool, dry place.

✓ **Incompatibilities:** Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.

- ✓ **Safety:** Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products, and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

5.15.4. Guar Gum :

- ✓ **Nonproprietary Names**
  BP: Guar Galactomannan
  PhEur: Guar Galactomannan
  USP-NF: Guar Gum
- ✓ **Synonyms:** E412; Galactosol; guar flour; guar galactomannanum; jaguar gum; Meyprogat; Meyprodor; Meyprofin.
- ✓ **Chemical Name and CAS Registry Number:** Galactomannan polysaccharide [9000-30-0]
- ✓ **Molecular formula:** $C_6H_{12}O_6$
- ✓ **Molecular mass :** ≈220 000
- ✓ **Description**: Almost white to pale yellowish white powder; odour, characteristic.
- ✓ **Functional Category**: Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.
- ✓ **Applications**: Guar gum is a galactomannan, commonly used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier.

Guar gum has also been examined for use in colonic drug delivery. Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations. Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus. It has also been used as an appetite suppressant, although its use for this purpose, in tablet form, is now banned in the UK.

- ✓ **Solubility:** When stirred with 50 parts of water, a thick jelly is formed which, with further addition of 150 parts of water, yields a thick transparent suspension; practically insoluble in ethanol(95%).
- ✓ **Stability:** Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.
- ✓ **Storage:** Guar gum powder should be stored in a well-closed container in a cool, dry place.
- ✓ **Incompatibilities:** Guar gum is compatible with most other plant hydrocolloids such as Tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum.
- ✓ **Safety**: It is generally regarded as a nontoxic and nonirritant material.

6. Materials & Methodology:

6.1. Materials & Equipments:

6.1.1. Materials:

Table No. 11: List of materials used.

Ingredients	Manufacturer/ Suppliers
Rosuvastatin calcium	SAIN Medicaments Pvt.Ltd., Hyderabad.
Calcium Phosphate,Tri basic	Loba Chemie Pvt. Ltd., Mumbai
Carbopol 934P	Loba Chemie Pvt. Ltd., Mumbai
HPMC K100	Loba Chemie Pvt. Ltd., Mumbai
Xanthan gum	Loba Chemie Pvt. Ltd., Mumbai
Guar gum	Loba Chemie Pvt. Ltd., Mumbai
Sodium Bicarbonate	Loba Chemie Pvt. Ltd., Mumbai
Citric acid	A to Z pharmaceuticals, Chennai.
Lactose	SD Fine chemicals Ltd., Mumbai
Magnesium Stearate	Loba Chemie Pvt. Ltd., Mumbai
Talc	SD Fine chemicals Ltd., Mumbai

6.1.2. Equipments:

Table No. 12: List of Equipments used.

Instruments	Manufacturer
Electronic Weighing balance	Shimadzu, Japan. (ELB300)
Sieves	Retsch, Hyderabad. (FR – 019)
Blender	Cadmach, Ahmadabad.
Friabilator	Electro lab, Mumbai. (EF-2)
UV-Visible spectrophotometer	Shimadzu, Japan. (UV-L700)
HPLC	Agilent technologies, Japan. (LC-10 Ai)
FTIR	Shimadzu, Japan. (8400S)
Differential Scaning Calorimetry	Universal V4.7A TA Instruments, USA. (DSC Q200 V24.4 Build 116)
Disintegration apparatus	Electrolab, Mumbai. (ED-04)
Digital Vernier calipers	Wenzhou Shahe, China. (0 -300mm;12)
Dissolution apparatus USP Type II	Electrolab, Mumbai. (TDL-08L)
Single punch machine	Shimadzu, Japan. (CMD3)
Hardness tester	Cadmach, Ahmadabad. (Monsanto)
Friability tester	Electro lab, Mumbai. (EF-TW)

6.2. Compatibility studies:

6.2.1. Procedure for FTIR analysis:

To study the compatibility of various formulation excipients with Rosuvastatin calcium, solid admixtures were prepared by mixing the drug with each formulation excipient separately. The solid admixtures were characterized using FTIR analysis (Shimadzu;8400S)

6.2.2. Other compatibility tests:

Drug is mixed with excipients in the ratio of 1:1. These mixtures were kept in a glass amber colored vials and packed properly. These vials are exposed to 40˚c / 75 % RH. Observations for physical appearance are made at initially, 2 week, and 4week, the samples were withdrawn for analysis of parameters like, Appearance, Assay.

6.3. Analytical Method Optimization:

6.3.1. Determination of λmax of Rosuvastatin in simple UV Spectrophotometric method: [68]

Rosuvastatin (100 mg) was accurately weighed and dissolved in 100 mL methanol to form a stock solution (1000 µg/mL). The stock solution was further diluted suitably with methanol to get a working standard solution of concentration 100 µg/mL. This working standard solution was suitably diluted to give a concentration of 14 µg/mL and this was then scanned in UV range (200-400nm).

6.3.2. Preparation of calibration curve of Rosuvastatin: [69]

Accurately weighed quantity of Rosuvastatin calcium (100 mg) was dissolved in 100ml of methanol in a 100 ml volumetric flask, and further dilutions were made by using methanol to obtain concentrations ranging from 25 to 75 µg/ml. Using a simple, rapid, and precise RP-HPLC method, the resultant peak areas of the drug were measured. Calibration curve was plotted between peak areas of drug against concentration of the drug.

6.4. Preformulation Studies: [70, 71]

Preformulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Table No. 13: The purpose of Ingredients and functions used for the formulation

Ingredients	**Functions**
Rosuvastatin calcium	Active ingredient
Carbopol 934	Polymer
HPMC K100	Polymer
Xanthan gum	Polymer
Guar gum	Polymer

6.4.1. Bulk density (Db):

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

Db = M / Vo…….Eq. No. 12

Where,

Db = Bulk density (gm/cc) ,

M = is the mass of powder (g),

Vo = is the bulk volume of powder (cc).

6.4.2. Tapped density (T.D): 10 gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 Ts from a constant height and tapped volume was read. It is expressed in gm/cc and is given by:

$$D_t = M / V_t \text{.....Eq. No. 13}$$

Where,

D_t = Tapped density (gm/cc)

M = is the mass of powder (g)

V_t = is the tapped volume of powder (cc)

6.3.3. Hausner's Ratio: It was determined by using the Following formula,

Hausner's Ratio = Tapped bulk density/ Loose bulk density…….Eq. No. 14

Table No. 14: Correlation between Hausner's ratio values and flow properties.

Hausner's ratio	Properties
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair and aid not needed
1.35-1.45	Poor must agitate
> 1.5	Poor
Above 2	Extremely Poor

6.4.4. Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = [(TD – BD) x 100]/BD……Eq. No. 3

Where,

TD is Tapped density,

BD is bulk density.

Table No. 15: Relation between Carr's index and powder flow characteristics

Carr's index (%)	Type of flow
5-15	Excellent
12-18	Good
18-23	Fair to possible
23-35	Poor
35-38	Very poor
>40	Extremely poor

6.4.5. Angle of repose (θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel until the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula:

$$\theta = \tan^{-1}(h/r) \quad \text{.....Eq. No. 15}$$

Where,

θ = angle of repose

h = height of pile,

r = radius of the base of the pile.

Table No. 16: Comparison between Angle of repose and flow property

Angle of Repose	Flow property
< 25	Excellent
25 – 30	Good
30 – 40	Moderate
> 40	Poor

6.5. Formulation Preparation: [72]

6.5.1. Preparation of Rosuvastatin calcium floating tablets:

Tablets containing 150 mg Rosuvastatin calcium were prepared, according to the design depicted in table-5, by direct compression method. The respective powders, namely Rosuvastatin calcium, release-retarding polymer(s) Xanthan gum,Guar gum,HPMC K100 and Carbopol 934, a gas-forming agent (Sodium Bicarbonate), and all excipients as given in table -5 were passed through sieve no. 20, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. Magnesium Stearate and talc were then added to the mixed powders. Mixing was continued for another 3 min. Finally, 150 mg of each mixture were weighed and fed manually into the die of a single punch tableting machine and compressed. The hardness of the tablets was adjusted at 4- 5 kg/cm^2 using a Monsanto hardness tester.

6.5.2. Steps in Direct Compression Procedure:

- **Screening:**

Weigh all ingredients except the lubricant and screen them (20 - 45 mesh screen). Add the low density material first and the high density material at the end. It is beneficial to combine materials with poor flowability, small particle size or static charge with another material in order to improve the overall handling of the powder blend. Sometimes a pre-blending step is done to facilitate screening.

- **Mixing:**

Mix the powder blend to achieve content uniformity. Add the lubricant to the powder blend and mix for 2 - 5 minutes (avoid over mixing and over lubrication).

- **Compression:**

Compress the powder blend to target weight and hardness.

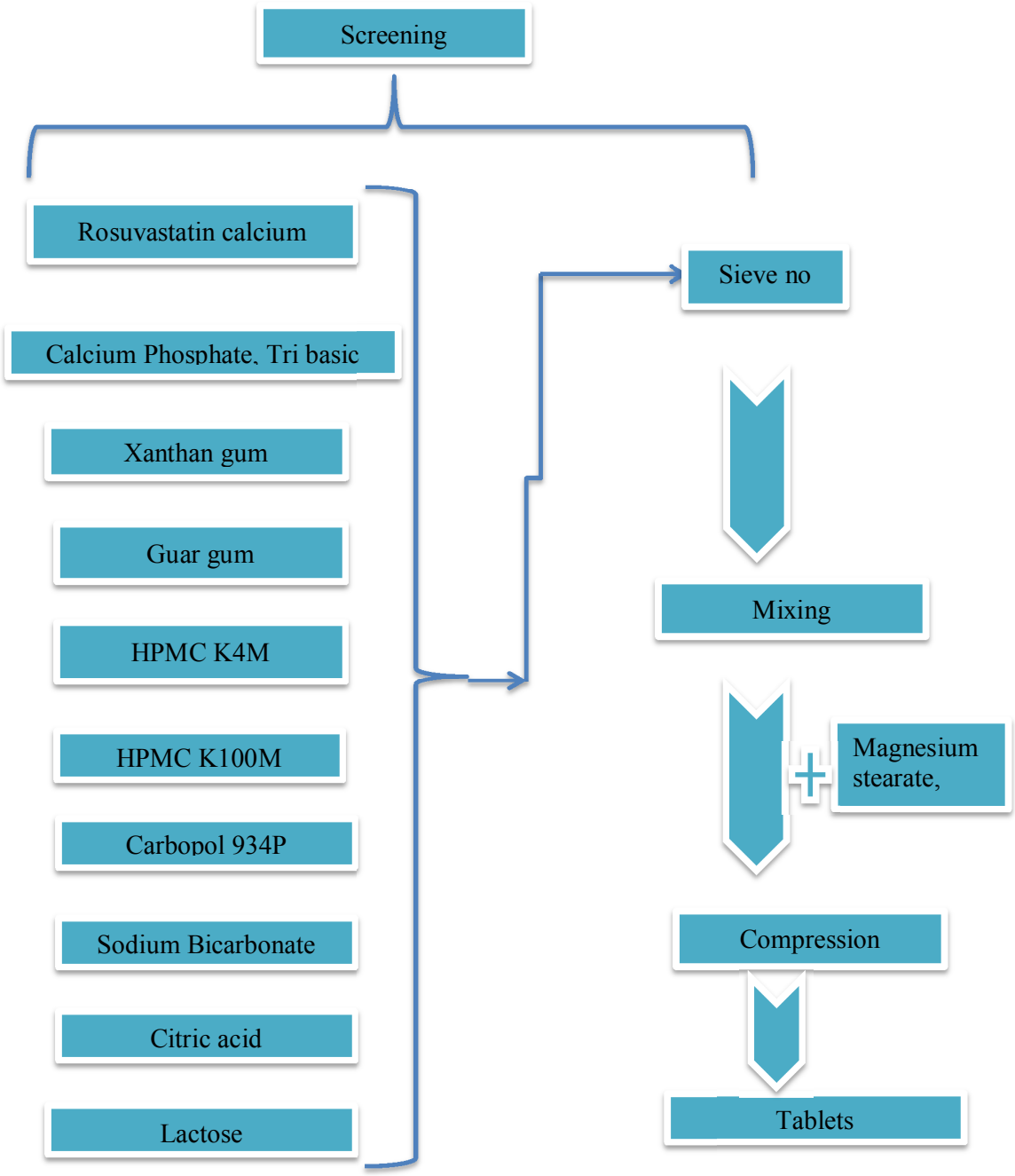


Fig. No. 31: Schematic representation of Preparing Floating tablets

Table No. 17: The composition of the investigated Rosuvastatin calcium floating matrix tablets (in milligrams).

Name of the material	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1. Rosuvastatin calcium	40	40	40	40	40	40	40	40	40	40
2. Tri basic calcium phosphate	10	10	10	10	10	10	10	10	10	10
3. Xanthan gum	10	15	20							
4. Guar gum				10	15	20				
5. HPMC K4M	20	25	30	20	25	30				
6. HPMC K100M							30	30	20	20
7. Carbopol 934P							20	10	10	10
8. Sodium Bicarbonate	10	20	30	10	20	30	20	20	25	30
9. Citric acid	10	10	10	10	10	10	10	10	10	10
10. Magnesium stearate	5	5	5	5	5	5	5	5	5	5
11. Talc	5	5	5	5	5	5	5	5	5	5
12. Lactose	40	20	-	40	20	-	20	30	35	30
Total tablet weight	150mg									

6.6. Evaluation Parameters for Rosuvastatin calcium tablets:

6.6.1. Post Compression physical parameters:

- **Thickness and diameter:**

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Digital Vernier calipers. It is measured in mm.

- **Hardness:**

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

➢ **Friability (F):**

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4mint), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{W_{intial} - W_{final}}{W_{intial}} \times 100$$

…….Eq. No. 16

➢ **Weight variation:**

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

$$PD = \frac{W_{avg} - W_{intial}}{W_{avg}} \times 100$$

.....Eq. No. 17

Where,

PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = individual weight of tablet.

Table No. 18: IP standards of uniformity of weight

Average weight of tablet	**% of deviation**
≤ 80 mg	10
> 80 mg to <250 mg	7.5
≥ 250 mg	5

6.7. Procedure for Uniformity of drug content and Assay of Rosuvastatin calcium floating matrix tablets:

6. 7. 1. Prepretion of standard solution:

Weigh a quantity of 40mg standard Rosuvastatin calcium powder and transfere into 100ml volumetric flask and dilute it to 100ml with methanol, pippet out 1 ml of the above solutiion to 40ml volumetric flask and make up the volume with methanol, which gives 10µgm/ml concentration solution.

6. 7. 2. Prepretion of Sample solution:

Twenty tablets of Rosuvastatin calcium were weighed and powdered. Weigh a quantity of the tablet powder equivalent to 40mg of Rosuvastatin calcium and transfer into 100ml volumetric flask and dilute it to 100ml with methanol, pippet out 1 ml of the above solutiion to 40ml volumetric flask and make up the volume with methanol.

The absorbance of the above standard and sample was measured using UV spectroscopy at 244nm.

6.8. Tablet floating behavior:[73]

The floating behavior of the tablets was visually determined, in triplicate, a tablet was placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ^{0}C. The floating lag time ‘‘the time between tablet introduction and its buoyancy” and total floating duration ‘‘the time during which tablet remains buoyant” were recorded.

6.9. Tablet swelling ability:[73]

The swelling behaviour of the tablets was determined, in triplicate. A tablet was weighed (Wo) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ^{0}C. At regular time intervals, the tablet were removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (Wt). The swelling index (SI) was calculated using the formula.

% Swelling Index = {(Wt) – (Wo)/ (Wo)} x 100……..Eq. No. 18

where,

Wt = is the weight of the swollen tablet,

Wo = is the initial weight of the tablet.

6.10. In-vitro Drug release studies:

Table No. 19: Dissolution parameters:

Dissolution medium	0.1 N HCl
Temperature	37± 0.5 ^{0} C
RPM	50
Vol. withdrawn and replaced	5 ml every 1 hr
λ max	244 nm
Blank solution	0.1 N HCl
Duration of study	24 hr
Volume of dissolution media	900 ml

Drug release studies of the prepared floating tablets as well as the commercially available tablets were performed, in triplicate, in a USP Dissolution Tester Apparatus, type- II (Paddle method) (VK 7000 Dissolution Testing Station), at 37 ± 0.5 _C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 mL of 0.1 N HCl solution (pH 1.2). Aliquots of 5 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 244 nm, as mentioned before. At each time of withdrawal, 5 mL of fresh medium was replaced into the dissolution flask.

6.11. Kinetic Analysis of In-Vitro drug release:

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

6.11.1. Zero order kinetic model – Cumulative % drug released versus T.

6.11.2. First order kinetic model – Log cumulative percent drug remaining versus T.

6.11.3. Higuchi's model – Cumulative percent drug released versus square root of T.

6.11.4. Korsmeyer Equation / Peppa's Model – Log cumulative percent drug released versus logT.

6.11.5. Hixon - crowell cube root Law - Cube root of the percentage of drug remaining in the matrix Vs time.

6.11.1. Zero order kinetics:

Zero order release would be predicted by the following equation:

$$\mathbf{At = A_0 - K_0 t \ldots\ldots\ldots\ldots\ldots\ldots Eq.\ No.\ 19}$$

Where,

At = Drug release at Time "t".

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr-1).

When the data is plotted as cumulative percent drug release versus Time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K_0.

6.11.2. First Order Kinetics:

First order release would be predicted by the following equation:

$$\mathbf{Log\ C = log\ C_0 - K_t / 2.303 \ldots\ldots\ldots\ldots\ldots Eq.\ No.\ 20}$$

where,

C = Amount of drug remained at Time "t".

C_0 = Initial amount of drug.

K = First – order rate constant (hr-1).

When the data is plotted as log cumulative percent drug remaining versus T yields a straight line, indicating that the release follow first order kinetics. The constant „K" can be obtained by multiplying 2.303 with the slope values.

6.11.3 Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi‟s classical diffusion equation.

$Q = [D\varepsilon / T (2 A - \varepsilon Cs) Cst]1/2$……Eq. No. 21

where,

Q = Amount of drug released at time "t".

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

Ɛ= Porosity of the matrix.

T= Tortuosity.

t= Time (hrs) at which "q‟ amount of drug is released.

Above equation may be simplified if one assumes that "D", "Cs", and "A", are constant. Then equation becomes:

$Q = Kt_{1/2}$……Eq. No. 22

When the data is plotted according to equation i.e. cumulative drug release versus square root of T yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to "K" (Higuchi's 1963).

6.11.4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the sustained – release matrix tablets, the release data were also fitted to the well known exponential equation (Korsmeyer equation / Peppa‟s law equation),

This is often used to describe the drug release behavior from polymeric systems.

$Mt / Ma = K_t n$……Eq. No. 23

Where,

Mt / Ma = the fraction of drug released at time "t",

K = Constant incorporating the structural and geometrical characteristics of the Drug / polymer system.

N = Diffusion exponent related to the mechanism of the release. Above equation can be simplified by applying log on both sides,

And we get: Log Mt / Ma = Log K + n Log t

When the data is plotted as log of drug released versus log T, yields a straight line with a slope equal to „n" and the „K" can be obtained from y intercept. For Fickian release "n" = 0.5 while for anomalous (non–Fickian) transport "n" ranges between 0.5 and 1.0. The mechanism of in-vitro drug release study was shown below:

Table No. 20: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

"n" Value	**Drug release**
0.45	Fickian release
0.45 < n < 0.89	Non – Fickian/anomalous release
n > 0.89 < 1	Class II transport
n >1	Supercase transport

6.11.5. Hixoncrowell cube root Law:

The Hixson-Crowell cube root law, describesthe release from systems where there is a change in surface area and diameter of particles or tablets (Erosion Mechanism)

- **Hixson-crowell rate equation:**

$$Q_{01/3} - Q_{t1/3} = KHCt\text{……..Eq. No.}$$

Where,

Qt is the amount of drug released in time t,

Q_0 is the initial amount of the drug in tablet and

KHC is the rate constant for Hixson- Crowell rate equation as the cube root of the percentage of drug remaining in the matrix Vs time.

6.12. Stability Study: [74,75]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications are addressed in ICH guidelines.

7. Results and Discussion:

7. 1. Rosuvastatin and excipients Compatibility Studies:

7. 1. 1. Rosuvastatin and excipients compatibility studies by FTIR Spectroscopy:

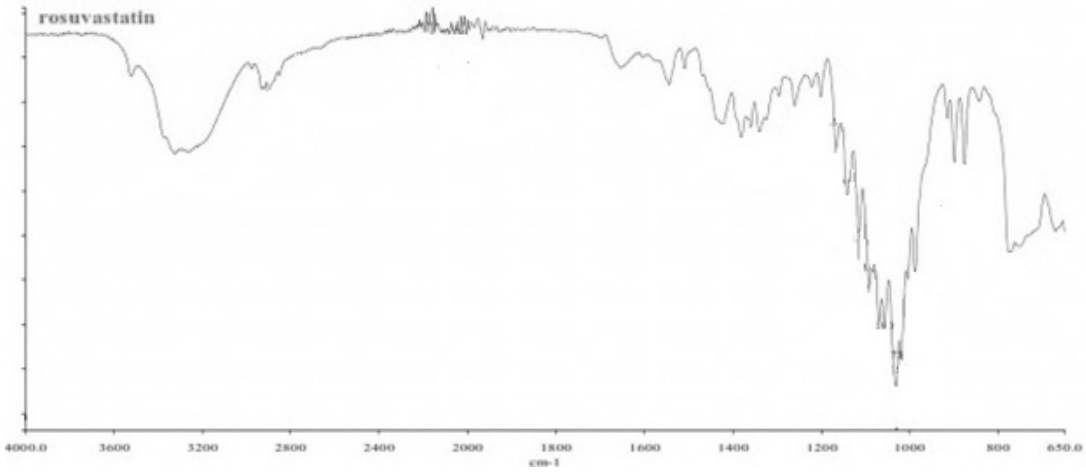


Fig. No. 32: FTIR Spectrum of Rosuvastatin calcium

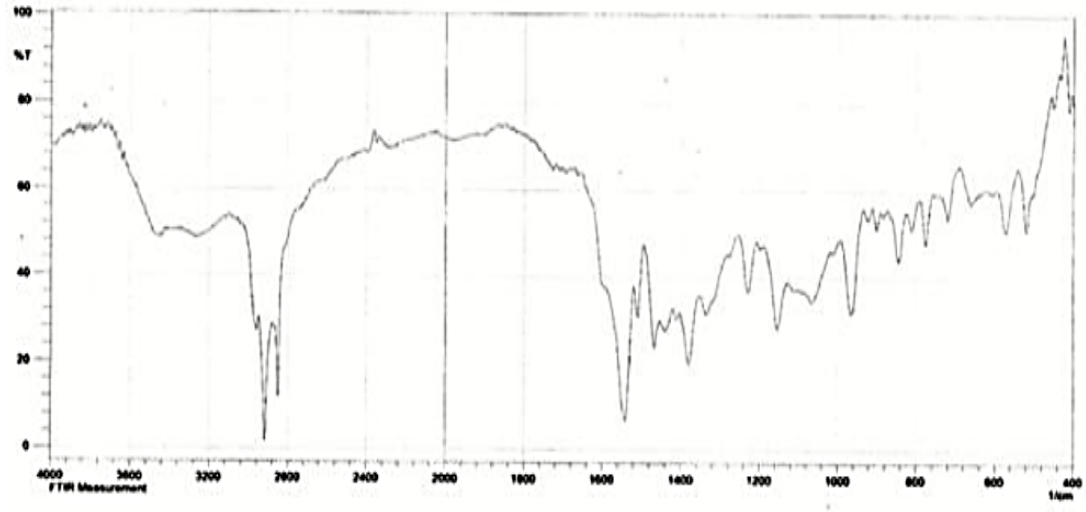


Fig. No. 33: FTIR Spectrum of Optimized batch (F10)

7. 1. 2. Drug and excipients compatibility studies by Physical appearance and Assay:

Table No. 21: Differnet ratios of drug and excipients taken for Compatibility Study.

Name of the Excipients	Ratio	Assay (%)	Final observation		Conclusion
			40 ° C / 75 % RH		
			2nd week	4th week	
Rosuvastatin calcium	-	98.04	No colour Change	No colour change	Compatible
Rosuvastatin calcium : Tri basic calcium phosphate	1:1	99.46	No colour change	No colour change	Compatible
Rosuvastatin calcium : Xanthan gum	1:1	98.84	No colour change	No colour change	Compatible
Rosuvastatin calcium : Guar gum	1:1	98.08	No colour change	No colour change	Compatible
Rosuvastatin calcium : HPMC K4M	1:1	97.47	No colour change	No colour change	Compatible
Rosuvastatin calcium : HPMC K100M	1:1	99.02	No colour change	No colour change	Compatible
Rosuvastatin calcium : Carbopol 934P	1:1	98.44	No colour change	No colour change	Compatible
Rosuvastatin calcium : $NaHCO_3$	1:1	99.47	No colour change	No colour change	Compatible
Rosuvastatin calcium : Citric acid	1:1	98.29	No colour change	No colour change	Compatible
Rosuvastatin calcium : Magnesium stearate	1:1	97.26	No colour change	No colour change	Compatible
Rosuvastatin calcium : Talc	1:1	99.48	No colour change	No colour change	Compatible
Rosuvastatin calcium : Lactose	1:1	99.06	No colour change	No colour change	Compatible

7.2. Characterization of Rosuvastatin and polymers by DSC analysis:

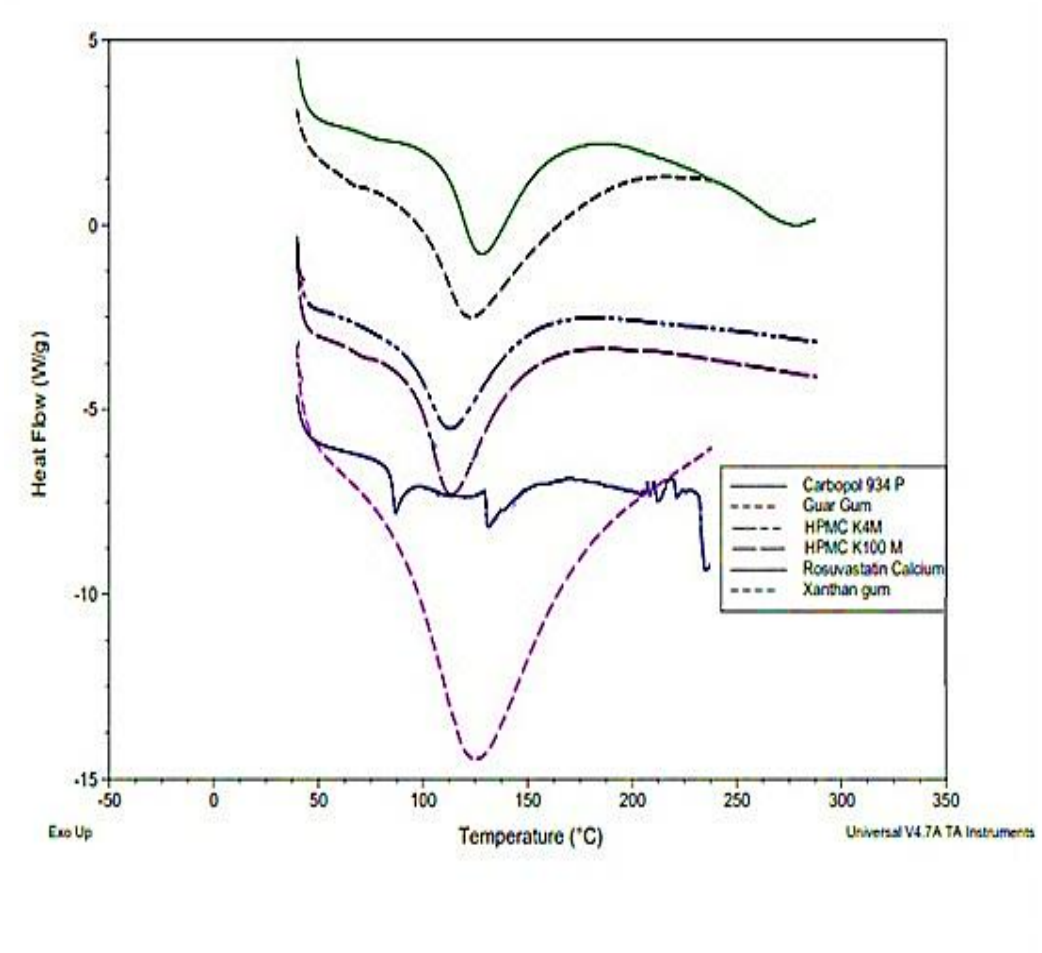


Fig.No. 34: Characterization of pure Rosuvastatin and Polymers by DSC Thermogram

7.3. Determination of **λmax of Rosuvastatin** *by Simple U.V. Spectrophotometric method:*

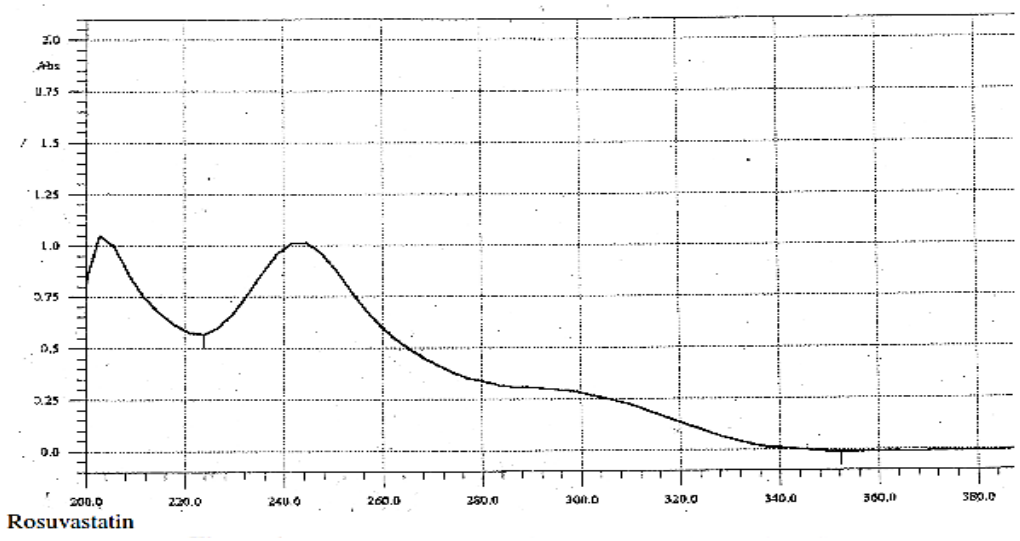


Fig. No. 35: U.V. spectrum of Rosuvastatin calcium in methanol.

21) λmax of Rosuvastatin = 244nm

7.4. Calibration curve of Rosuvastatin calcium:

Table No. 22: Calibration of Rosuvastatin calcium

Nominal Concentration (µg/mL)	AVG Peak area	Practical concentration (µg/mL)	Accuracy (%)
25	1186360	25.01	100.08
30	1421245	29.98	99.96
40	1895067	40.01	100.03
50	2369727	50.05	100.10
60	2847064	60.14	100.25
70	3324742	70.25	100.36
75	3530504	74.60	99.47

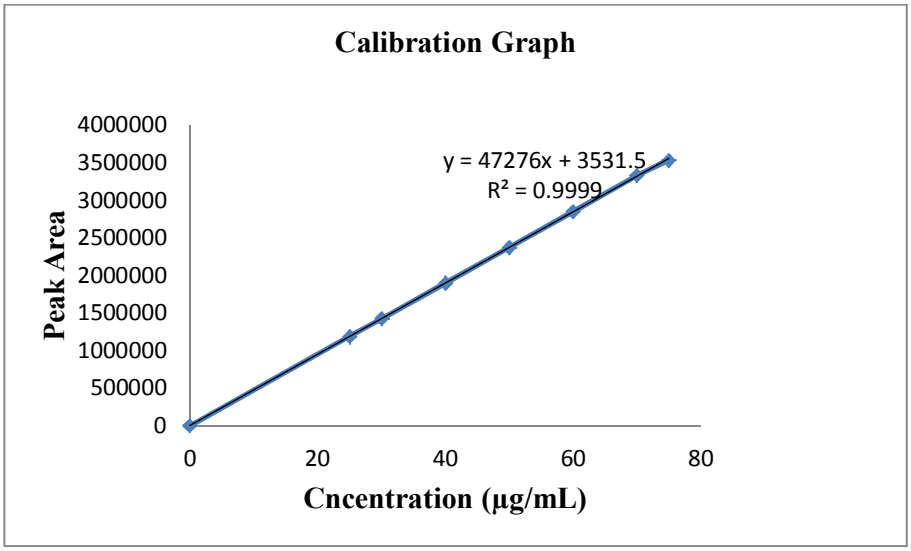


Fig. No. 36: Calibration curve of Rosuvastatin calcium in methanol at 244 nm

7. 5. Preformulation:

7. 5. 1. API characterization:

Table No. 23: Preformulation parameters of blended Rosuvastatin powder:

Parameters	Mean readings
Bulk Density	0.67
Tapped Density	0.86
Carr's index	22.09
Hausner's ratio	1.28
Angle of repose	36.5^0

7. 5. 2. Flow properties:

Table No. 24: Flow properties of blended formulations:

Formulation Code	Blend Characterization				
	Bulk density (BD) (g/cc)	**Tapped density (TD) (g/cc)**	**Compressibilty Index (%)**	**Hausner's ratio**	**Angle of repose**
F1	0.468 ± 0.009	0.586 ± 0.013	20.13 ± 1.49	1.25 ± 0.03	24.55 ± 1.53
F2	0.464 ± 0.004	0.583 ± 0.012	20.41 ± 1.64	1.25 ± 0.04	28.98 ± 1.57
F3	0.464 ± 0.003	0.584 ± 0.015	20.54 ± 1.34	1.26 ± 0.04	29.85 ± 1.44
F4	0.472 ± 0.005	0.589 ± 0.014	19.86 ± 0.76	1.24 ± 0.08	25.30 ± 1.45
F5	0.466 ± 0.006	0.584 ± 0.017	20.20 ± 0.87	1.25 ± 0.06	28.97 ± 1.58
F6	0.469 ± 0.004	0.588 ± 0.0019	20.23 ± 1.36	1.25 ± 0.04	29.13 ± 1.23
F7	0.490 ± 0.009	0.594 ± 0.013	17.50 ± 1.49	1.21 ± 0.06	29.85 ± 1.44
F8	0.486 ± 0.003	0.586 ± 0.015	17.06 ± 1.34	1.21 ± 0.08	25.98 ± 1.57
F9	0.486 ± 0.004	0.578 ± 0.012	15.67 ± 1.62	1.18 ± 0.04	24.41 ± 1.53
F10	0.484 ± 0.004	0.581 ± 0.013	16.69 ± 1.64	1.20 ± 0.04	24.55 ± 1.53

7.6. Post compressional parameters:

7.6.1. Physical characteristics of Rosuvastatin calcium floating matrix tablets:

Table No. 25: Physical characteristics of Rosuvastatin calcium floating matrix tablets:

Formulation Code	Physical properties		
	Weight variation (mg)	**Hardness (Kg/cm^2)**	**Diameter (mm)**
F1	150 ± 0.46	4.8± 0.34	7 ± 0.01
F2	150 ± 0.64	4.3± 0.15	7 ± 0.12
F3	150 ± 0.48	4.2 ± 0.44	7 ± 0.14
F4	150 ± 0.60	5.6 ± 013	7 ± 0.14
F5	150 ± 0.38	5.6 ± 0.34	7 ± 0.23
F6	150 ± 0.64	5.9 ± 0.15	7 ± 0.26
F7	150 ± 0.55	5.9 ± 0.23	7 ± 0.18
F8	150 ± 0.54	5.3 ± 0.17	7 ± 0.10
F9	150 ± 0.53	5.2 ± 0.14	7 ± 0.04
F10	150 ± 0.42	5.2± 0.49	7 ± 0.08

Table No. 26: Physical characteristics of Rosuvastatin calcium floating matrix Tablets

Formulation Code	Physical properties		
	Thickness (mm)	**Friability (%)**	**Drug content (mg)**
F1	3.19 ± 0.01	0.339 ± 0.011	39.65
F2	3.17 ± 0.14	0.352 ± 0.014	39.26
F3	3.20 ± 0.08	0.410 ± 0.012	39.24
F4	3.14 ± 0.04	0.328 ± 0.016	38.31
F5	3.16 ± 0.06	0.340 ± 0.01	38.18
F6	3.21 ± 0.13	0.350 ± 0.24	38.97
F7	3.15 ± 0.17	0.225 ± 0.42	39.83
F8	3.16 ± 0.06	0.246 ± 0.23	39.27
F9	3.22 ± 0.05	0.251 ± 0.15	39.40
F10	3.23 ± 0.03	0.286 ± 0.38	39.52

7.7. Floating behavior of Rosuvastatin calcium Floating Matrix Tablets:

Table No. 27: Floating behavior of tablets with Sodium Bicarbonate.

Formulation Code	Parameter		
	Amount of $NaHCO_3$	**Floating lag time (sec)**	**Floating duration (Hrs)**
F1	10	86	> 10
F2	20	77	> 10
F3	30	64	> 10
F4	10	84	> 10
F5	20	73	> 10
F6	30	62	> 10
F7	20	58	> 10
F8	20	63	> 10
F9	25	60	> 10
F10	30	54	> 10

Fig. No. 37. Photographs taken during *in vitro* buoyancy study of formula F10 in 200 mL 0.1N HCl at different time intervals.

7.8. Swelling index of Rosuvastatin calcium Floating Matrix Tablets:

Table No. 28: Swelling Index of tablets:

Formulation Code	Time (Hrs)				
	1	**2**	**4**	**6**	**8**
F1	58.46	89.38	141.65	189.52	199.86
F2	68.75	97.47	163.41	213.76	225.39
F3	79.43	119.59	177.66	228.53	243.69
F4	32.74	70.87	132.94	174.88	181.57
F5	54.63	86.36	141.88	183.36	195.49
F6	67.71	99.47	157.59	198.58	218.38
F7	49.83	67.69	104.71	121.77	135.25
F8	36.55	52.31	89.43	99.50	117.74
F9	34.79	55.27	83.33	104.26	119.56
F10	37.47	56.76	84.47	101.51	125.32

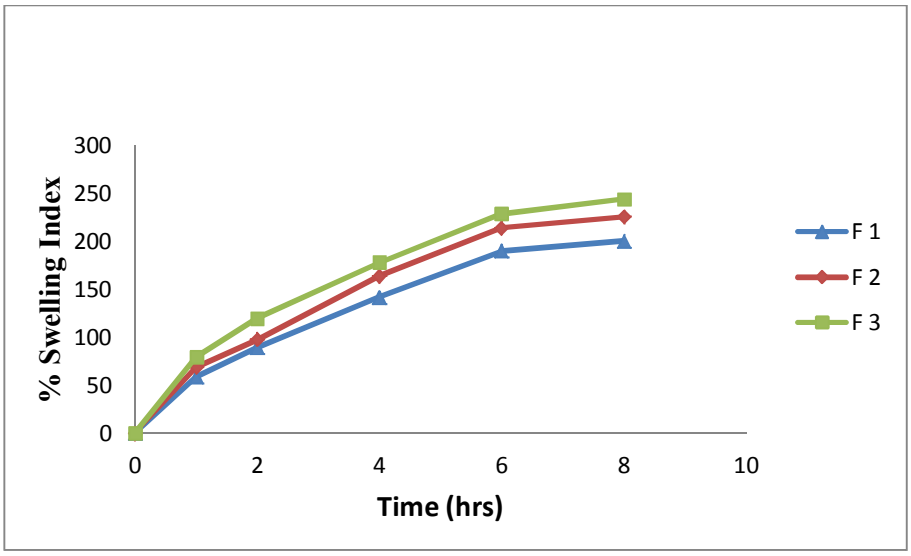


Fig. No. 38: Comparitive Swelling Index for F1, F2 & F3

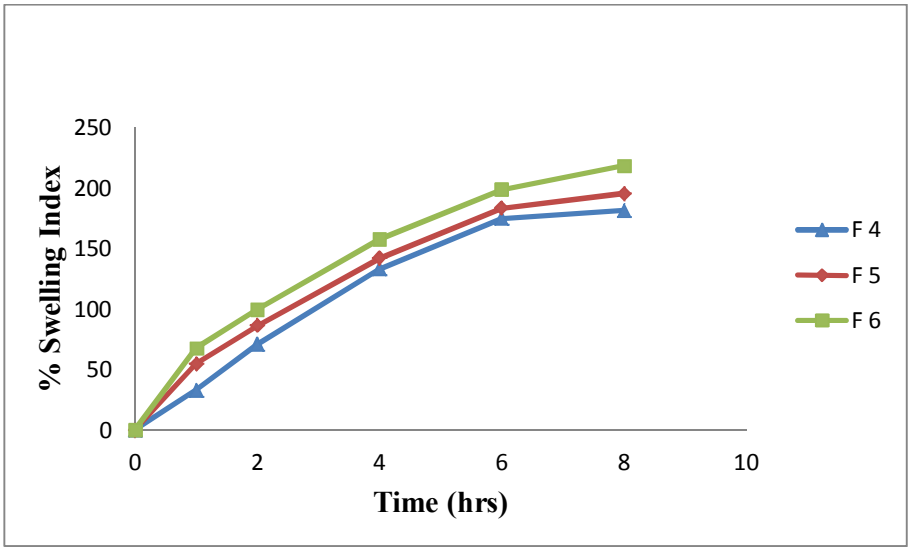


Fig. No. 39: Comparitive Swelling Index for F4, F5 & F6.

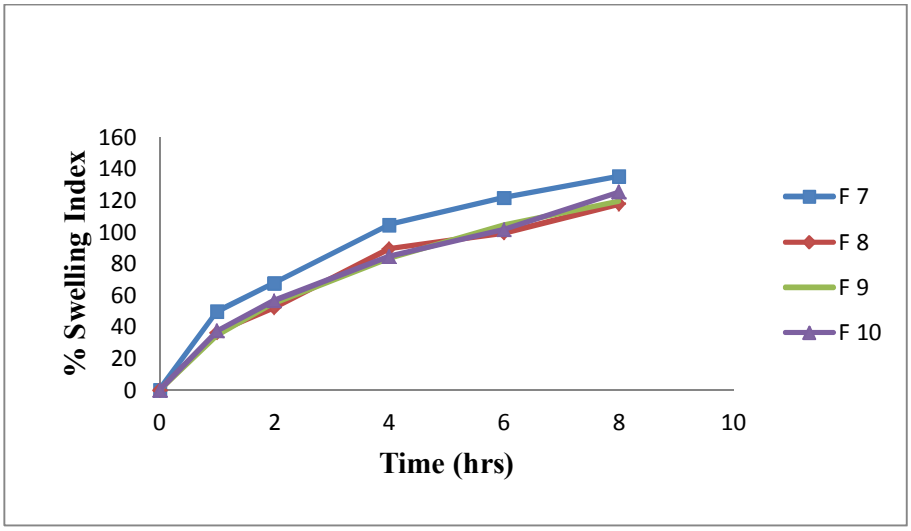


Fig. No. 40: Comparitive Swelling Index for F7, F8, F9 & F10.

7.9. In Vitro Dissolution Studies of Rosuvastatin calcium Floating Matrix Tablets:

Table No. 29: *In Vitro* drug release of *Rosuvastatin calcium Floating Matrix Tablets* (F1 to F6):

Time (hr)	% Drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	11±1.39	9± 1.32	8± 1.62	10±1.62	7± 1.39	6± 1.95
4	37±1.55	35±0.89	33±1.55	34±1.25	31±1.63	27±1.07
8	59±1.32	56±1.63	54±1.65	56±1.63	52±1.83	46±1.19
12	83±1.63	81±1.19	79±1.39	80±0.89	78±1.39	63±1.19
16	91±1.42	90±1.55	87±1.19	88±1.19	85±1.63	78±1.19
20	99±1.06	99±1.25	95±1.32	99±1.63	93±0.89	85±1.39
24	-	-	99±0.89		99±1.25	93±1.42

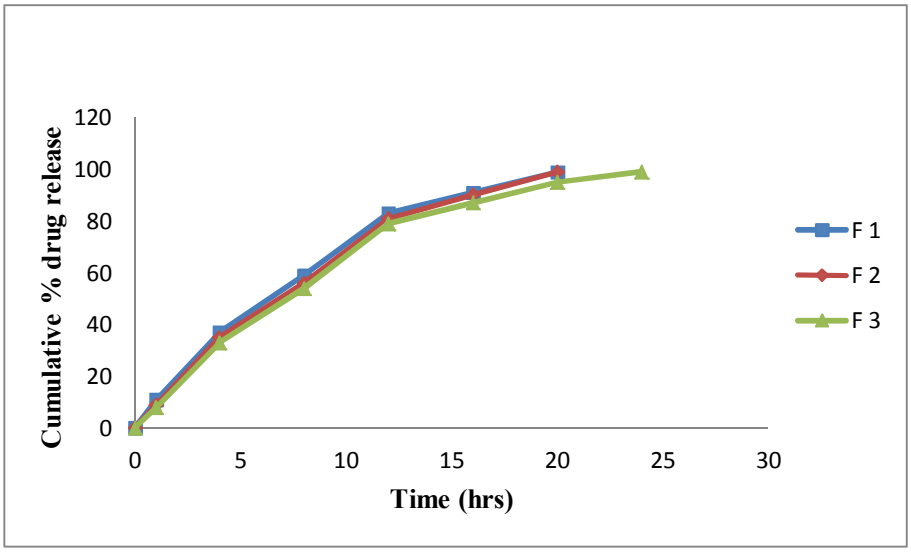


Fig. No. 41: Comparitive dissolution profile for F1, F2 & F3

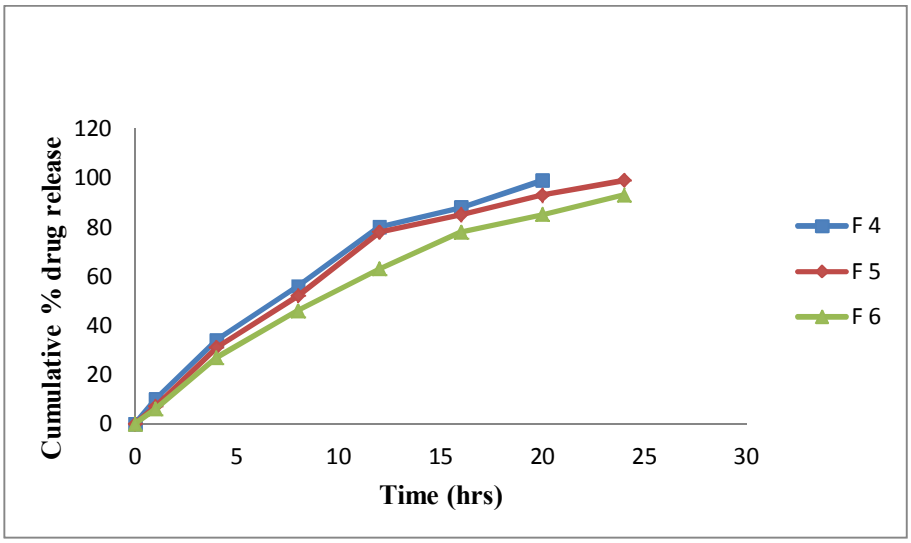


Fig. No. 42: Comparitive dissolution profile for F4, F5 & F6

Table No. 30: *In Vitro* drug release of *Rosuvastatin calcium Floating Matrix Tablets* (F7 to F10):

Time (hr)	% Drug release			
	F7	**F8**	**F9**	**F10**
1	2± 1.77	4± 1.51	6± 1.57	7± 1.57
4	13± 1.32	18± 1.05	26± 1.32	22± 1.46
8	24± 1.07	31± 1.23	48± 1.83	39± 1.63
12	37± 1.62	47± 1.63	65± 1.69	54± 1.28
16	49± 0.89	56± 1.62	79± 1.19	71± 1.09
20	55± 1.55	73± 1.83	87± 1.25	88± 1.42
24	68± 1.63	84± 1.19	99± 1.55	99± 1.69

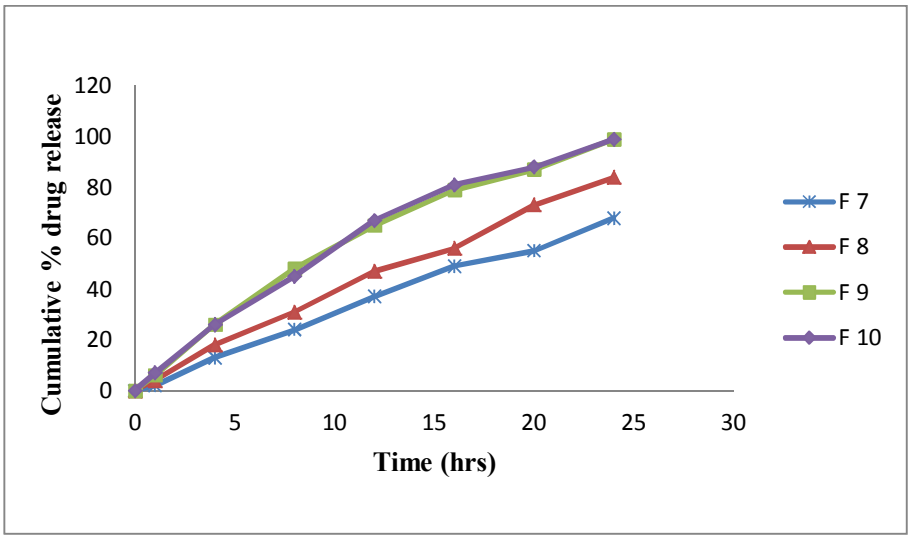


Fig. No. 43: Comparitive dissolution profile for F7, F8, F9 & F10.

7. 10. Drug release kinetics of Rosuvastatin calcium Floating Matrix Tablets *:*

Table No. 31: Regression co-efficient (R^2) values of drug release data obtained from various kinetic models and Release exponent (n) values from Korsmeyer-Peppas.

Formulation Code	kinetic models					
	Zero order	**First order**	**Higuchi**	**Korsmeyer-Peppas**		**Hixson-crowell**
	R^2	**R^2**	**R^2**	**R^2**	**n**	**R^2**
F1	0.939	0.935	0.990	0.987	0.746	0.994
F2	0.948	0.919	0.992	0.985	0.812	0.996
F3	0.913	0.965	0.981	0.976	0.802	0.988
F4	0.955	0.897	0.992	0.991	0.773	0.994
F5	0.919	0.942	0.982	0.976	0.837	0.989
F6	0.957	0.979	0.996	0.985	0.862	0.996
F7	0.993	0.985	0.979	0.989	1.093	0.995
F8	0.995	0.951	0.997	0.996	0.945	0.989
F9	0.966	0.856	0.998	0.988	0.877	0.990
F10	0.996	0.872	0.992	0.993	0.838	0.993

7. 10. 1. Graphs of drug release kinetics for optimized batch (F10):

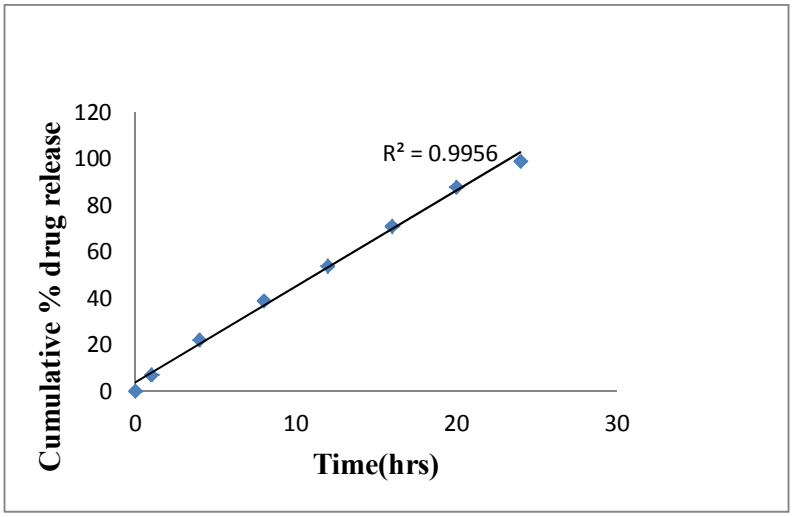


Fig. No. 44: Zero order kinetics

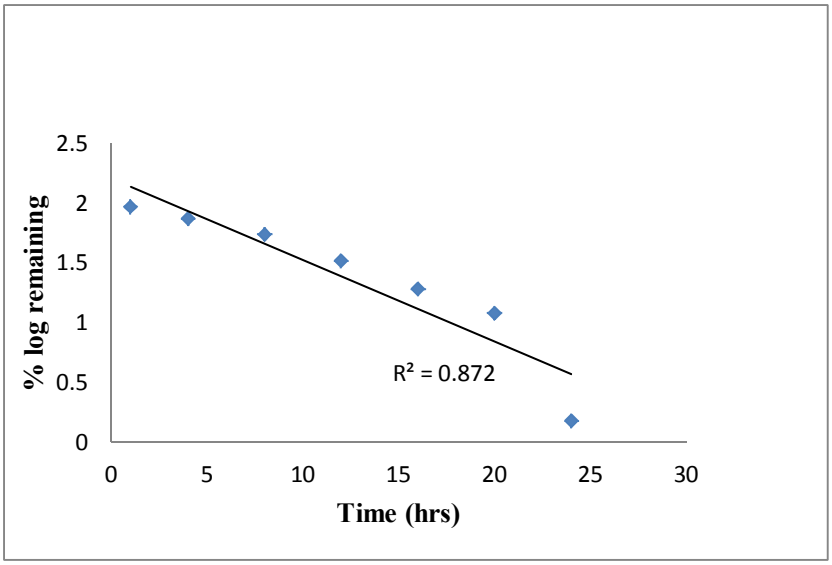


Fig. No. 45: First order kinetics

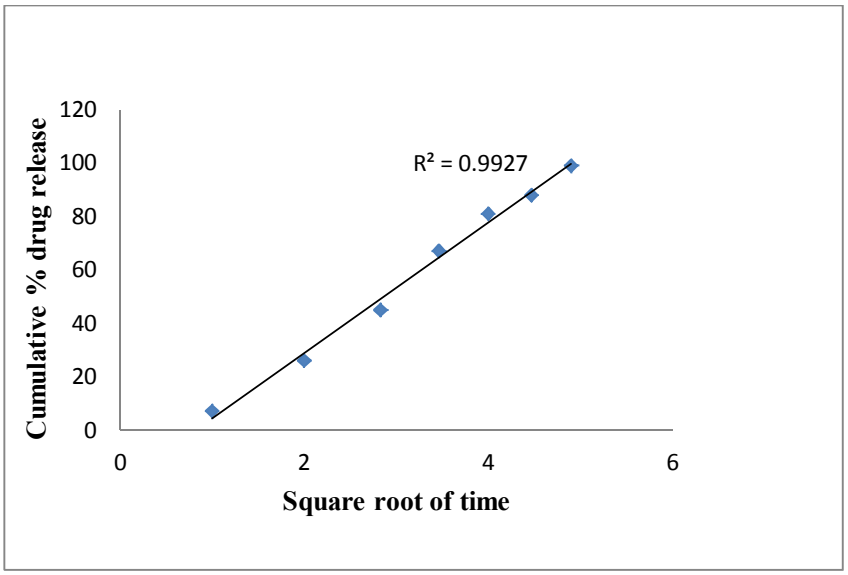


Fig. No. 46: Higuchi drug release kinetics

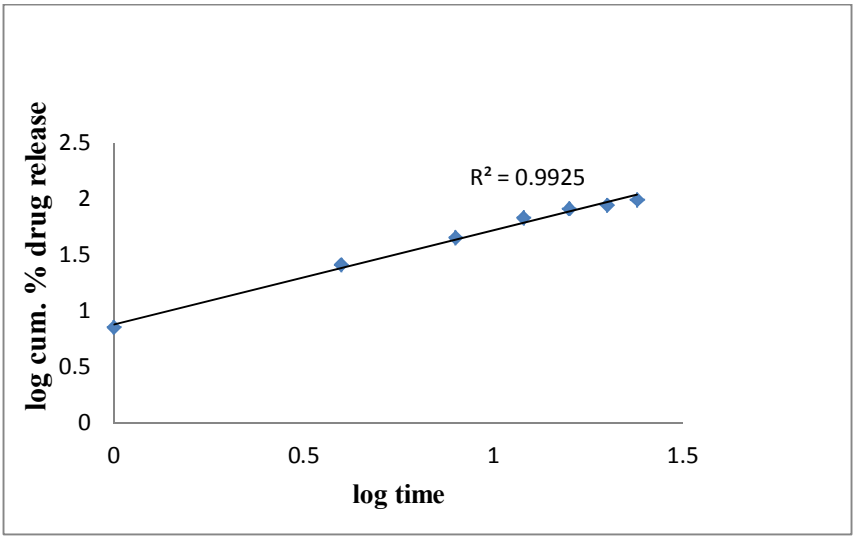


Fig. No. 47: Krosmeyer - peppas drug release kinetics

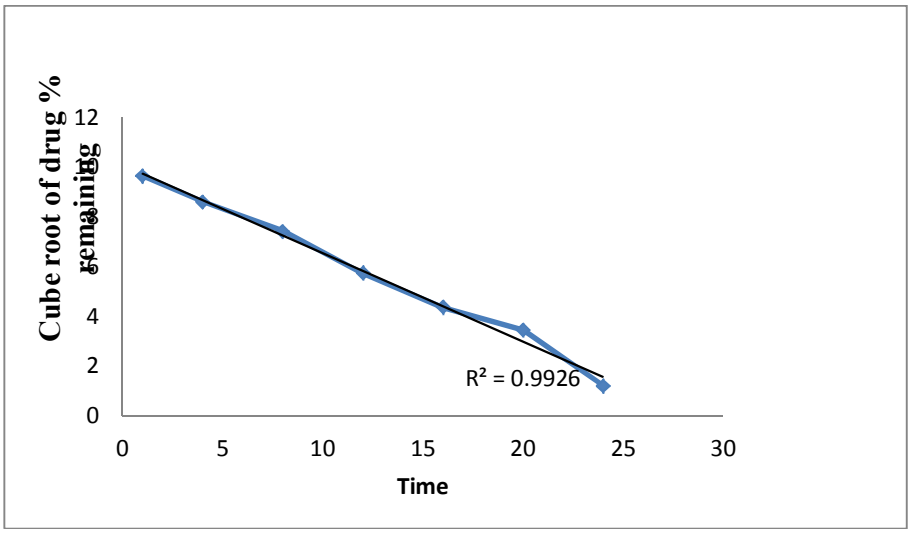


Fig. No. 48: Hixson-crowell drug release kinetics

7. 11. Stability studies:

Table No. 32: Stability studies for optimized formulation (F10):

Parameters	Duration		
	After 15 days	**After 30 days**	**After 45 days**
Physical appearance	No change	No change	No change
Weight variation (mg)	150 ± 1.26	150 ± 1.44	149 ± 0.86
Hardness (Kg/cm^2)	5.2 ± 0.89	5.1 ± 1.18	4.9 ± 0.45
Diameter (mm)	7 ± 0.08	7 ± 0.16	6.9 ± 0.03
Friability (%)	0.286 ± 0.82	0.431 ± 0.03	0.524 ± 0.12
% Drug content at $25^0C/65\%RH$	99.46 ± 0.43	98.86 ± 0.62	98.73 ± 0.91
% Drug content at $25^0C/70\%RH$	99.26 ± 0.26	98.42 ± 0.18	98.25 ± 0.28
% Drug content at $40^0C/65\%RH$	98.88 ± 0.21	98.34 ± 0.32	98.16 ± 0.44
% Drug content at $40^0C/70\%RH$	98.36 ± 0.32	98.16 ± 0.41	97.89 ± 0.16
Bouyancy lag time (sec)	55 ± 1.23	56 ± 2.20	56 ± 3.13
Duration of Bouyancy (Hrs)	> 10	> 10	> 10

7. 12. Discussion:

Oral route of administration is the most widely accepted route of delivery due to the ease of administration, avoidance of pain and other risks of parenteral administration and has good patient compliance. The main advantage of the oral sustained release dosage form is that it maintains the therapeutic concentration over an extended period of time. Several new technologies have been developed to overcome the physicochemical and pharmacokinetic characteristic of drugs, while improving the patient compliance. One of these technologies is the Floating matrix type of dosage forms.

7. 12. 1. Formulation development:

Rosuvastatin Calcium is a lipid lowering agent, which is used for the treatment of Dyslipidemia. Because of it's severe adverse effects, side effects, deleterious in high plasma concentration have been made to develop a controlled release formulation to maintain the Therapeutic Index. Due to moisture sensitive nature of Rosuvastatin and to prepare matrix tablets in cost effective and easy manner here preffered Direct compression method. HPMC K 100 M, Carbopol 934P, Xanthan gum, Guar gum polymers, which swell and form a hydrogel matrix, when comes in contact with aqueous solutions and facilitates Floating Drug Delivery System, which is effectively deliver Sparingly soluble drugs (Rosuvastatin) used in this study. Here Sodium Bicarbonate is used as gas generating agent.

Calcium Phosphate Tri basic and Lactose Anhydrous were used as tablet diluents and their effect on the drug release was studied. Calcium Phosphate Tri basic is stabilizing agent for Rosuvastatin and it will prevent the Lactone formation, Oxidation decomposition products. Lactose Anhydrous is used as a diluent in this Direct Compression method, because of moisture sensitivity of Rosuvastatin.

7. 12. 2. Drug and excipients compatibility studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Through FTIR analysis, The IR spectra of Rosuvastatin calcium is characterized by the absorption frequency of two stretching band at 3394.72 cm^{-1} and that of carbonyl group at 1604.77 cm^{-1}. The results indicate that has no interactions or bondings between drug and polymers/excipients, so there was no chemical incompatibility between drug and excipients used in the formulation.

And the vials, in which the drug and excipients are in different ratio exposed to 40˚c / 75 % RH and observed physical appearance, made at initially, 2 week, and 4week. The samples were not change in colour. From the Assay of solid admixtures samples also gives good percentage of drug content. So it's showing good compatibility for the formulation development with the mentioned polymers and excipients.

7. 12. 3. Charachterization of Rosuvastatin and polymers by DSC analysis:

Rosuvastatin and polymers were identified by DSC analysis, the characteristic peaks indicating melting points of Rosuvastatin, HPMC K100M, Carbopol 934P, HPMC K4M, Xanthan gum, Guar gum are 129.38°c, 142.78°c, 153.96°c, 142.30°c, 154.85°c and 162.51°c respectively.

7. 12. 4. Determination of λmax of Rosuvastatin in simple UV Spectrophotometric method:

The method showed an absorption maximum for Rosuvastatin calcium at 244 nm, the λ max which is similar to the obtained reference (244 nm) and the result showed in **Figure No. 36.**

7. 12. 5. Calibration curve of Rosuvastatin calcium:

The results from HPLC method showed that, there was an excellent correlation and linearity between peak area and analyte concentration. The linearity result showed in **Table No 22.**

7. 12. 6. Flow Properties:

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values

of Carr's Index (Compressibility) 12 to 18 % usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the powders were in the range from 17.50 ± 1.49, 17.06 ± 1.34, 15.67 ± 1.62, 16.69 ± 1.64 (F7, F8, F9, F10) hence exhibit good flow characteristics. Values of angle of repose are rarely 20^o and values up to 40^o indicate reasonable flow properties. Above 50^o however the powder flows only with great difficulties. Dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%. They are particularly sensitive to change in particle size distribution and to the moisture content, and they provide a rapid significant batch to batch differences in these respects. The angle of repose of the powders were in the range of 29.85 ± 1.44, 25.98 ± 1.57, 24.41 ± 1.53, 24.55 ± 1.53 (F7 – F10) which indicate a good flow property of the powders. Here the angle of repose was found to be below 40^o. This shows that the reasonable flow property of powders. The results are shown in **Table No. 24.**

7. 12. 7. Evaluation of Rosuvastatin calcium Floating Matrix Tablets:

2. Physical Parameters (Shape, Size, Hardness & Friability):

The shape and size of the tablets were found to be within the limit. The results are given in **Table No. 25 & 26.** The hardness of the tablets was found to be in the range of 5.2 ± 0.15 to 5.9 ± 0.23 Kg/ cm^2. It was within the range of monograph specification. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

3. Weight Variation:

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations twenty tablets were randomly selected and weighed. The results are given in **Table No. 26.** The average weights of the tablets were found to be within the prescribed official limits (IP).

4. Drug content Uniformity:

Drug content for each of the formulations was estimated. The drug content for all the batches was found to be in the range of 99.45 to 101.40 %. The results are given in **Table No. 26.**

7. 12. 8. Effect of Gas generating agent (Sodium Bicarbonate) on Floating lag time and Floating duration:

The investigated gastric floating systems employed Sodium Bicarbonate as a gas-forming agent dispersed in a hydrogel matrix (HPMC K100, Carbopol 934P, Xanthan gum, Guar gum). The buoyancy study revealed the ability of most formulae to maintain buoyant more than 10 h **(Table No. 27** and **Fig. 41**). This suggests that the gel layers, formed by the investigated polymers, enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it float on the test medium (0.1 N HCl) for this extended period of time. These matrices are fabricated so that upon arrival in the stomach, carbon dioxide gas is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. A decrease in specific gravity causes the dosage form to float on the chime. The extended residence time of drug in stomach could cause increased absorption due to the fact that the stomach and upper intestine was the main absorption site for Rosuvastatin calcium. One of the factors influencing the behavior of the effervescent systems is their floating lag time. As shown in **Table No. 27.** The floating lag time of formula F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 are 86, 77, 64, 84, 73, 62, 58, 63, 60 and 54seconds .This could be explained with regard to the rate of the test medium penetration into these matrices and consequently the time required for gel formation. From the above results concluded that as the percentage of Sodium Bicarbonate increases, the floating lag time decreases. This phenomenon might be due to the generation of larger amounts of effervescence with higher Sodium Bicarbonate percentages. This would lead to an increase in the rate of pore formation and consequently rapid hydration of the tablet's matrices. It is worth to note that high amount of Sodium Bicarbonate containing formulae (F10) have shorter floating lag time than the corresponding formulae prepared with low amount of Sodium Bicarbonate.

7. 12. 9. Swelling Behavior:

The hydration ability of the formula is important because it influences: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers as HPMC K100, Carbopol 934, Xanthan gum, Guar gum in contact with the test fluid and (iii) drug release kinetics. It could be concluded that the test medium uptake of the prepared matrices depends on the type of polymer **(Figures 35, 36, 37)**. Formulaton 1

showed the highest swelling indices throughout the study period. This may be related to the high affinity of Xanthan gum containing matrices to the test medium. The maximum swelling index of this formula 243.69 was achieved after 8 h. The maximum swelling indices of F1, F2, F3, F4, F5, F6, F7, F8, F9and F10 formulae 199.86, 225.39, 243.69, 181.57, 195.49, 218.38, 135.25, 117.74, 119.56, 125.32 **(Table. No. 28)** were achieved after 8 h. Throughout the study period, low the swelling indices was achieved with formula F9 & F10. This could be related to the lower affinity of Carbopol 934 containing matrices to the test medium. As reported by Bertram and Bodmeier, the ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. Peppas and Khare suggested that the swelling equilibrium (maximum swelling index) is reached when the osmotic forces of the functional groups are balanced by the restrictive forces of the higher ordering of the polymer chains. As the water continues to enter the tablet, a highly concentrated polymer solution is formed, denoted as a gel layer. The solvent continues to penetrate the tablet, and the gel layer and the dimensions of the swollen tablet increase, a process normally referred to as the swelling process. In a parallel line, Ju et al. suggested that a polymer concentration gradient is formed in the tablet, starting at a high concentration in the more or less dry core and declining through the gel layer towards the gel layer surface. At the surface of the gel layer, denoted as the erosion front, the polymer concentration is assumed to correspond to the critical polymer concentration.

7. 12. 10. *In- vitro* studies of Rosuvastatin Calcium Floating matrix tablets:

Depending on the type and concentration of the investigated polymer(s) in the current study, variable drug release profiles were successfully tailored. Tablets formulated using guar gum and xanthan gum alone and combine were eroded faster and dissolved completely within 14 - 16 hr, while tablet containing HPMC remain intact and provided slow release up to 20-24 hr. The influence of HPMC K100, Carbopol 934, Xanthan gum, Guar gum on the release of Rosuvastatin calcium from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 ^{0}C was shown in **Fig. No. 38, 39, 40.** It was clear that all formulae succeeded in controlling the rate of drug release. However, the drug release rate was dependent on the type and concentration of the investigated polymer(s). At 12 hr the percentage of drug release

of F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 83± 1.63, 81± 1.19, 79 ±1.39, 80± 0.89, 78± 1.39, 63± 1.19, 37± 1.62, 47± 1.63, 65± 1.69 and 67± 1.28 respectively. At 20 Hr the percentage of drug release of F1,F2, F3, F4,F5, F6, F7, F8, F9 and F10 formulations were found as 99± 1.06, 99± 1.25, 95± 1.32, 99± 1.63, 93± 0.89, 85± 1.39, 55± 1.55,73± 1.83,87± 1.25 and 88± 1.42 respectively. At 24 Hr the percentage of drug release of F3, F5, F6, F7, F8, F9 and F10 formulations were found as 99± 0.89, 99± 1.25, 93± 1.42, 68± 1.63, 84± 1.19, 99± 1.55 and 99± 1.69 respectively.

7. 12. 11. Effect of Xanthan gum and HPMC K4M polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F1, F2, F3, which are containing 20%, 26%, 33% of the polymer mixture of Xanthan gum and HPMC K4M, showing good swelling behavior but formulation F3 only succeeded in controlling the rate of drug release for 24hrs.

7. 12. 12. Effect of Guar gum and HPMC K4M polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F4, F5, F6, which are containing 20%, 26%, 33% of the polymer mixture of Guar gum and HPMC K4M, showing good swelling behavior and Floating duration (more than 10hrs) and F5 only succeeded in controlling the rate of drug release for 24hrs. The F6 formulation showing only ≈85% drug release at 24hr. So we can conclude that from the first six formulations (F1 – F6), increase in amount of polymer/ viscosity results decrease in drug release rate.

7. 12. 13. Effect of HPMC K100M and Carbopol 934P polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F7, F8, F9, F10 which are containing 33%, 26%, 20%, 20% of the polymer mixture of Guar gum and HPMC K4M showing much lower drug diffusivity. F9, F10 formulations, which are having less amount of polymer mixture succeeded in controlling the rate of drug release for 24hrs, because of the higher viscosity of Carbopol 934, HPMCK100M would promote the synergic effect, formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann and Peppas suggested that the drug release from Carbopol 934P and HPMC K100M matrices is

sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibitions into the matrix. (ii) Due to the imbibition of water, polymers swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially.

It is worth to note that, sometimes a burst effect was observed with all formulations. This could be due to the fact that the gel layer, which controls the drug release rate, needs some time to become effective . The rapid drug dissolution from the surface of the tablets could be another possible explanation.

Interestingly, this effect was less predominant with those formulae have synergic effect of carbopol 934P and HPMC K100M amount. Formation of gel like networks surrounding these matrices, upon contact with aqueous media, would produce strong surface barriers that would effectively reduce the burst drug release. Taking into consideration the goal of the work of achieving a compromise between excellent floating behaviour (very short floating lag time and prolonged floating duration), extended gastro retentive period and sustained drug release characteristics, formula F9 was chosen for further studies. The formulation (F10), which is containing highest gas-forming agent concentration showed the highest drug release rate and short Floating Lag time than F9 formulation. The elevation of the gas-forming agent concentration would generate larger amounts of effervescence leading to an increase in the rate of pore formation, rapid hydration of the tablets matrices and consequently a faster drug release rate.

7. 12. 14. Drug Release Kinetics for Rosuvastatin Calcium Floating Matrix tablets:

Different models like Zero order, First order, Higuchi's, and Peppa's were drawn for the formulations. The results of linear regression analysis of data including regression coefficient are summarized in **Table No. 31** and **Figure No. 44 - 48.** When the regression coefficient 'R^2' value of zero order and first order plots were compared, it was observed that the 'R^2' values of zero order were in the range of 0.913 to 0.995 whereas the 'R^2' values of first order plots were found to be in the range of 0.856 to 0.985 indicating drug release from all the formulations were found to follow zero

order kinetics. The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the predominant mechanism limiting drug release since the 'R^2' values of Higuchis plots were nearer to linearity (0.985-0.996). Korsmeyer-Peppas plots, slope equal to "n" states that kind of drug release, $0.45 < n < 0.89$, Non – Fickian/anomalous release for the optimized formulation F10. From the drug release kinetics stuy the optimized formulation F10 gives the "R^2" values, Zero order (0.965), First order (0.872), Higuchi (0.992), Korsmeyer-Peppas (0.838), so it has concluded that formulation follows zero order controlled release and Diffusion controlled mechanism.

7. 12. 15. Stability studies:

Stability studies were conducted for the optimized formulation F10. The stability study was performed at 25^0C/65%RH, 25^0C/70%RH, 40^0C/65%RH, 40^0C/70%RH for a specific period of time. The tablets were analysed for Physical appearance, Weight variation, Hardness, Diameter, Friability, Drug content, Bouyancy lag time, Duration of Bouyancy. The overall results showed that the formulation is stable at the above mentioned storage conditions. shown in **Table No. 32.**

8. Summary:

In this present study Controlled-release effervescent floating matrix tablets of Rosuvastatin calcium were prepared by direct compression technique, using HPMC K100, Carbopol 934P, Xanthan gum, Guar gum as release retardant components. Different parameters like hardness, friability, weight variation, drug content uniformity, Floating lag time and duration, swelling index and in-vitro drug release were evaluated for these formulations . The hardness of the floating tablets was adjusted in the current work ≈ 4 - 5 kg/cm^2. The thickness of all tablet batches ranged from ≈3.2mm. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ≈150 ± 0.66mg. All the prepared formulae meet the USP requirements. Drug uniformity results were found to be good among different batches. The percentage of drug content ranged from 99.65% to 101.40%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

The floating lag time of formula F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 are 86,77, 64, 84, 73, 62, 58, 63, 60 and 54 seconds. This could be explained with regard to the rate of the test medium penetration into these matrices and consequently the time required for gel formation. From the above results concluded that as the percentage of Sodium Bicarbonate increases, the floating lag time decreases. *Invitro* drug released studies were evaluated for 24 hr. At 12 hr the percentage of drug release of F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 83 ± 1.63, 81± 1.19,79 ±1.39, 80 ± 0.89, 78 ± 1.39, 63 ± 1.19, 37 ± 1.62, 47 ± 1.63, 65 ± 1.69 and 67 ± 1.28 respectively. At 20hrs the percentage of drug release of F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 99 ± 1.06, 99 ± 1.25, 95 ± 1.32, 99± 1.63, 93± 0.89, 85± 1.39, 55± 1.55, 73± 1.83, 87± 1.25 and 88± 1.42 respectively. At 24hrs the percentage of drug release of F3, F5, F6, F7, F8, F9 and F10 formulations were found as 99 ± 0.89, 99 ± 1.25, 93± 1.42, 68 ± 1.63, 84 ± 1.19, 99 ± 1.55 and 99± 1.69 respectively (Values have shown in **Table. No. 29 & 30**). It was found that increase in the concentration of HPMC K100, Carbopol 934, Xanthan gum,Guar gum decreases the drug release.

Polymers swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug must diffuse. This property makes them useful ingredients for sustained release matrix tablet. All the formulations have shown good sustained drug release and the formulations F7 to F10 containing Carbopol 934P and HPMC K100M have shown better controlled effect for 24 hr than other formulations. Those formulations have synergic effect of carbopol 934P and HPMC K100M amount in retarding drug release, reduce rapid drug dissolution from surface of the tablets.

Different models like Zero order, First order, Higuchi's, and Peppa's were drawn for the formulations. The results of linear regression analysis of data including regression coefficient are summarized in **Table. No. 31 and Figure. No. 44 - 48.** When the regression coefficient 'R^2' value of zero order and first order plots were compared, it was observed that the 'R^2' values of zero order were in the range of 0.913 to 0.995 whereas the 'R^2' values of first order plots were found to be in the range of 0.856 to 0.985 indicating drug release from all the formulations were found to follow zero order kinetics. The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the predominant mechanism limiting drug release since the 'R^2' values of Higuchis plots were nearer to linearity (0.981-0.998), Hixsoncrowell range is between 0.988 – 0.996. Korsmeyer-Peppas plots, slope equal to"n" states that kind of drug release, $0.45 < n < 0.89$,Non – Fickian/anomalous release for the optimized formulation F10.

9. Conclusion:

The Rosuvastatin Calcium Floating matrix tablets were prepared and evaluated. The Gastric Residence Time (GRT) of the tablet was considerably increased up to 24hrs time by optimizing the polymer concentration. The release was sustained up to 20hrs with 1: 1.5 ratio of HPMC K4M and Xanthan gum, but the Floating Lag time was found to be more with the combination.

Similarly, the combination between HPMC K4M and Guar gum also controlled the release more than 20hrs was observed. The combination between HPMC K100M and Carbopol 934P with the ratio of 2:1 was found to be satisfactory with release profile. Hence the Formulation F10 was optimized by for further studies. The formulation (F10) also satisfies the Swelling Index, Buoyancy time controlled the drug release up to 24hrs. The mechanism of drug release followed the Zero order kinetics with the co-efficient (R^2) value 0.996. Therefore, further studies with optimized formulation under progress in the lab.

References:

1) A.Pandey, A Review on current approaches in Gastro Retentive Drug Delivery System. Asian Journal of Pharmacy and Medical Science, (2012), 2(4).

2) Chein YW, Potential developments and new approaches in Oral Controlled Release Drug Delivery Systems, (1983), p. 1294-1330

3) S.Gopalakrishnan, Floating Drug Delivery Systems/ Journal of Pharmaceutical Science and Technology Vol. 3 (2), 2011, 548-554.

4) R. Garg, G.D. Gupta, Progress in controlled Gastro Retentive Delivery Systems, Trop. J. Pharm. Res. 7 (3) (2008), 1055–1066.

5) Chein YW, Controlled and Modulated Drug Delivery Systems, Encyclopedia of Pharmaceutical Technology. New York: Dekker; 1990, p. 281-313.

6) Kitamura S, Maeda K, Wang Y, Sugiyama Y. Involvement of Multiple Transporters in the Hepatobiliary Transport of Rosuvastatin. Drug Metabolism And Disposition. 2008 July, 36(10).

7) M.D. Chavanpatil, P. Jain, S. Chaudhari, R. Shear, R.R. Vavia, Novel sustained release, Swellable and Bioadhesive, Gastro Retentive Drug Delivery System for Ofloxacin, Int. J. Pharm. 316 (1–2) (2006), 86–92.

8) S.J. Hwang, H. Park, K. Park, Gastric retentive drug-delivery systems, Crit. Rev. Ther. Drug Carrier Syst. 15 (3) (1998), 243–284.

9) P.R. Seth, J. Tossounian, The Hydrodynamically Balanced System, a Novel Drug Delivery System for oral use, Drug Dev. Ind. Pharm. 10 (1984), 313–339.

10) L. Whitehead, J.T. Fell, J.H. Collett, Development of a Gastro Retentive Dosage form, Eur. J. Pharm. Sci. 4 (Suppl.) (1996), S182.

11) Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Itoh, Hollow microspheres for use as a Floating Controlled Drug Delivery System in the stomach, J. Pharm. Sci. 81 (1992), 135–140.

12) J. Chen, W.E. Blevins, H. Park, K. Park, Gastric retention properties of super porous hydrogel composites, J. Control. Release 64 (1-3) (2000), 39–51.

13) B.M. Singh, K.H. Kim, Floating Drug Delivery Systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Rel. 63 (2000), 235– 259.

14) Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins, Philadelphia, 2005 (electronic version).

15) M.Rosa, H. Zia, T.Rhodes, Dosing and testing *in-vitro* of a Bioadhesive and Floating Drug Delivery System for oral application, Int. J. Pharm. 105 (1994), 65–70.

16) Lapidus, H., Lordi, N.G., 1968. Drug release from compressed hydrophilic matrices. J. Pharm. Sci. 57, 1292–1301.

17) Ranga Rao, K.V., Padmalatha Devi, K., Buri, P., Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J. Controlled Release 12(1990), 133–141.

18) Shah, A.C., Design of oral sustained release drug delivery systems: *invitro*/ *in-vivo* considerations. In: Yacobi, A., Haperin-Walega, E. (Eds.), Oral Sustained Release Formulations Design and Evaluation. Pergamon Press, New York, (1988), pp. 35–56.

19) Shenouda, L.S., Adams, K.A., Zoglio, M.A., A Controlled Delivery System using two hydrophilic polymers. Int. J. Pharm. 61(1990), 127–134.

20) Robinson RR, Vincent HL. Controlled Drug Delivery. Vol. 20, 2nd ed. New York: Marcel Dekker Inc; 2009, p. 156-487.

21) Alderman DA. Swellable matrices as systems for oral Delivery. Int J Pharm and Prod Mfr. (1984), vol: 1-5.

22) Nigayale AG. Investigation of prolonged drug release from matrix formulation of chitosan. Drug Dev Ind Pharm. (1990), 16: 449-67.

23) Gomez AD. Role of water-uptake on tablet disintegration: design of improved method for penetration measurements, Acta Helv. (1986), 61(1):22-9.

24) Ahuja A., Khar R. K., Ali J., "Mucoadhesive Drug Delivery Systems." Drug Development and Industrial Pharmacy 23 (5) (1997), p. 489-515.

25) Kumar S, Jamil F, Rajput M, Sharma S. Gastro Retentive Drug Delivery System: Features and Facts. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012 Jan-March; 3(1).

26) Mathur P, Saroha K, Syan N. Floating Drug Delivery System: An innovative acceptable approach in Gastro Retentive Drug Delivery. Scholars Research Library. 2012 2(2).

27) Mishra A. Gastro Retentive Drug Delivery System: A Review. International Journal of Drug Development & Research. 2012 December; 4.

28) Pawar VK. Industrial Perspective of Gastroretentive Drug Delivery Systems: Physiochemical, Biopharmaceutical, Technological and Regulatory Consideration. Expert opinion on drug delivery. 2012;(9(5)): p. 551-565.

29) Shinde S. Gastro Retentive Drug Delivery System: A Review. International Journal of Pharmaceutical Research & Allied Sciences. 2012; 1(1).

30) J. Chen, W.E. Blevins, H. Park, K. Park, Gastric retention properties of super porous hydrogel composites, J. Control. Release 64 (1-3) (2000) 39–51.

31) Harland, R.S., Gazzinga, A., Sangalli, M.E., Colombo, P., Peppas, N.A., Drug/polymer matrix swelling and dissolution. Pharm. Res. 5, (1988) 488–494.

32) Lapidus, H., Lordi, N.G., Drug release from compressed hydrophilic matrices. J. Pharm. Sci. 57(1968), 1292–1301.

33) Brahma N. Singh, Kwon H. Kim, Floating drug delivery systems: an approach to Oral Controlled Drug Delivery via Gastric Retention, Journal of Controlled Release 63 (2000) 235–259 , www.elsevier.com/ locate / jconrel.

34) Kones R. Primary prevention of coronary heart disease:integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey. Drug Design, Development and Therapy. 2011; 5: p. 325-380.

35) Kitamura S. Involvement of Multiple Transporters in the Hepatobiliary Transport of Rosuvastatin. Drug Metabolism And Disposition. 2008 July; 36(10).

36) Arunkumar N, Rani C, Mohanraj K. Formulation and In Vitro evaluation of oral floating tablets of atorvastatin calcium. Research Journal Of Pharmacy And Technology. 2008 December; 1(4).

37) Dwivedi J, O.P.Mahatma. Formulation & Evaluation of Sustained Release Formulation of Rosuvastatin Calcium. Asian Journal of Biochemical and Pharmaceutical Research. 2011; 1(3).

38) Garg B, Gnanarajan G, Kothiyal P. Formulation and Evaluation of Pulsatile Drug Delivery System of Rosuvastatin Calcium Using Different Swelling Polymers. The Pharma Innovation. 2012; 1(7).

39) Krishnarajan D, Kumar NS, Jeyabalan G. Design And Evaluation Of Bioadhesive Tablets Of Rosuvastatin Calcium. International Journal of Biological & Pharmaceutical Research. 2012; 3(4).

40) Brahma N. Singh, Kwon H. Kim, Floating Drug Delivery Systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release 63 (2000) 235–259 ,www.elsevier.com/ locate / jconrel.

41) A. Streubel, J. Siepmann, R. Bodmeier*, Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release, European Journal of Pharmaceutical Sciences 18 (2003) 37–45, www.elsevier.com/ locate / ejps.

42) P.L. Bardonnet a,b, V. Faivre a,*, W.J. Pugh c, J.C. Piffaretti d, F. Falson, Gastroretentive dosage forms: Overview and special case of Helicobacter pylori, Journal of Controlled Release 111 (2006) 1 – 18, www.elsevier.com/locate/jconrel.

43) S.Gopalakrishnan, Floating Drug Delivery Systems/ Journal of Pharmaceutical Science and Technology Vol. 3 (2), 2011,548-554.

44) Ketan Gulabrao Albhar*, 2Vaibhav Sudhakar Wagh , 1Bhagwat Babasaheb Chavan, Effect of HPMC K4M, HPMC K15M, sodium alginate and carbopol 934 in the formulation of carbonyl iron capsule, Der Pharmacia Lettre, 2012, 4 (1):367-394.

45) Mina Ibrahim Tadros *, Controlled-Release Effervescent Floating Matrix Tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers journal homepage, European Journal of Pharmaceutics and Biopharmaceutics 74 (2010) 332–339 www.elsevier.com/locate/ejpb.

46) Amit Kumar Nayak *, Biswarup Das, Ruma Maji Gastroretentive Hydrodynamically Balanced Systems Of Ofloxacin: *In vitro* evaluation www.ksu.edu.sa, Saudi Pharmaceutical Journal (2011) ,www.sciencedirect.com.

47) PD Thahera1, Ashok1, K Latha2, T Shailaja2, S Nyamathulla3, MU Uhumwangho4 , Formulation And Evaluation of Norfloxacin Gastro Retentive Drug Delivery Systems using natural polymers http://www.icpjonline.com/documents/Vol1Issue7/01.

48) Tetsuo Hayashi a,b, Hideyoshi Kanbea,b, Minoru Okadaa,, *In vitro* and *in vivo* sustained-release characteristics of theophylline matrix tablets and novel cluster tablets International Journal of Pharmaceutics 341 (2007) 105–113.

49) Ian J. Hardy a,∗, Anne Windberg-Baarup b, Claudia Neri a, Paul V. Byway a, Steven W. Booth a, Shaun Fitzpatrick, Modulation of drug release kinetics from Hydroxy Propyl Methyl Cellulose matrix tablets using Poly Vinyl Pyrrolidone International Journal of Pharmaceutics 337 (2007) 246–253.

50) Praveen S. Hiremath, Ranendra N. Saha Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: Design and *in vitro* evaluations journal homepage: International Journal of Pharmaceutics 362 (2008) 118–125, www.elsevier.com/locate/ijpharm.

51) Ibrahim El-Bagory a,*, Nahla Barakat b, Mohamed A., Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: Design and *in vitro* evaluations International Journal of Pharmaceutics 362 (2008) 118 125www.ksu.edu.sa www.sciencedirect.com.

52) Giovanna Corti, Marzia Cirri, Francesca Maestrelli, Natascia Mennini, Paola Mura , Sustained-release matrix tablets of Metformin Hydrochloride in

combination with triacetyl-b-cyclodextrin European Journal of Pharmaceutics and Biopharmaceutics, 68 (2008) 303–309, www.elsevier.com/locate/ejpb.

53) Raghavendra rao, Gandhi sagar 1, patel tarun1 Formulation and evaluation of sustained release matrix tablets of Tramadol Hydrochlorid, International Journal of Pharmacy And Pharmaceutical Sciences vol1, suppl 1Non-Dec (2009).

54) Hiroyuki Kojima, Keiichi Yoshihara, Toyohiro Sawada, Hiromu Kondo, Kazuhiro Sako, Extended release of a large amount of highly water-soluble Diltiazem Hydrochloride by utilizing counter polymer in Poly Ethylene Oxides (PEO) / Poly Ethylene Glycol (PEG) matrix tablets journal homepage: www.elsevier.com/locate/ejpb , European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 556–562.

55) Gottimukkala Jayapal Reddy, Appa Rao Potu, Veerareddy Prabhakar Reddy, Raju Jukanti, Suresh Bandari Development and *in vitro-in vivo* Behaviour of Nizatidine Floating Tablets, Der Pharmacia Lettre, 2011, 3(1): 454-465.

56) www.Drugbank.com.

57) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 99–101.

58) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 782–784.

59) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 298–300.

60) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 326–329.

61) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 326–329.

62) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 110–113.

63) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 629–632.

64) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 181–183.

65) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 404–406.

66) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 728–730.

67) Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients,6th ed, Pharmaceutical Press, London, p. 359–361.

68) GUPTA A. Simple UV Spectrophotometric Determination of Rosuvastatin Calcium in Pure Form and in Pharmaceutical Formulations. E-Journal of Chemistry. 2009;(6(1)): p. 89-92.

69) Donthula S. A new validated RP-HPLC method for determination of Rosuvastatin calcium in bulk and pharmaceutical dosage form. Scholars Research Library. 2011;(3(3)): p. 350-356.

70) Lachmann L, Liebermann HA, Kiang JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese Publishing House (1998): p.430-40.

71) Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: tablets. 2nd ed:New York: Marcel Dekker, Inc.; 2005 (3) 77-160.

72) Pharmaceutical Polymers for Oral Solid Dosage Forms. Lubrizol.

73) Abed HN, Abdulrasool AA, Ghareeb MM. Controlled Release Floating Matrix Tablet of Captopril. Iraqi J Pharm Sci. 2011; 20(2).

74) International conference on harmonization (ICH) harmonized tripartite guideline for stability testing of new drugs substances and products Q1A (R2) aug-2003. Q1 (R2) Mar2004.

75) C.T.Rhodes, T.Cartesan. Drug stability principle and procedure, 3rd ed, New York, (2001).p.21-46.